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PTO 07-2287

Japanese Patent
02306916

BLOOD PLATELET ADHESION INHIBITOR

[Kesshōban Nenchaku Yokuseizai]

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UNITED STATES PATENT AND TRADEMARK OFFICE
Washington, D.C. March 2007

Translated by: Schreiber Translations, Inc.

Country	:	Japan
Document No.	:	02306916
Document Type	:	A
Language	:	Japanese
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Applicant	:	Otsuka Pharmaceutical Co., Ltd.
IPC	:	A61K 31/415, 31/425, 31/44, 31/445; C07D 235/18, 235/30, 277/66, 277/82, 401/12, 409/00, 417/00
Application Date	:	May 22, 1989
Publication Date	:	December 20, 1990
Foreign Language Title	:	Kesshōban Nenchaku Yokuseizai
English Title	:	BLOOD PLATELET ADHESION INHIBITOR

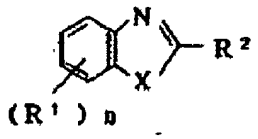
Specification /1[1]

Title

Blood Platelet Adhesion Inhibitor

Claims

(1) A blood platelet adhesion inhibitor characterized by comprising an active ingredient in the form of a benzazole compound, or a salt thereof, having the general formula:



[wherein X denotes a sulfur atom or the group  (wherein R^3 denotes a hydrogen atom, lower alkyl group, lower alkenyl group, or phenyl lower alkyl group);

R^1 denotes a halogen atom; cyano group; cyano-substituted lower alkoxy group; optionally halogen-substituted lower alkyl group; lower alkanoyl group; lower alkoxy group; hydroxyl group; nitro group; amino group; hydroxyl-substituted lower alkyl group; phenyl lower alkyl group optionally substituted on the phenyl ring with one to three groups selected from the group consisting of lower alkyl groups and hydroxyl groups; furyl lower alkoxy group optionally comprising a cycloalkyl group on the furyl ring; lower alkoxycarbonyl lower alkoxy group; aminothiocarbonyloxy group optionally substituted with a lower alkyl group; aminocarbonylthio group optionally substituted with a lower alkyl group; phenyl lower alkoxy group optionally substituted on the phenyl ring with one to three members selected from the group consisting of halogen atoms, lower alkyl groups, and hydroxyl groups; pyrrolidinyl lower alkyl group optionally comprising a substituent on the pyrrolidinyl ring in the form of a lower alkyl group having a hydryxol group; amidino group optionally substituted with a phenyl lower alkyl group optionally substituted on the phenyl ring with a

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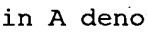
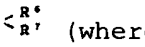
halogen atom; amidino lower alkoxy group optionally substituted with a lower alkyl; or  (wherein A denotes a lower alkyl group; m denotes 0 or 1; each of R^4 and R^5, which may be identical or different, denotes a hydrogen atom; phenyl lower alkyl group optionally substituted on the phenyl ring with a halogen atom; lower alkanoyl group optionally substituted with a halogen atom; lower alkyl group optionally substituted with a hydroxyl group or halogen atom; cycloalkyl group; or the group  (wherein l denotes 0 or 1; B denotes a lower

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[1] Numbers in the margin indicate pagination in the foreign text.

alkylene group; each of R^6 and R^7, which may be identical or different, denotes a hydrogen atom or lower alkyl group; and R^6 and R^7 may be optionally intercalated, together with the nitrogen atom to which they are bound, through a nitrogen atom to form a five or six-membered saturated hetero ring, there optionally being on said hetero ring a substituent in the form of an amino group substituted with a lower alkyl group); and R^4 and R^5 may be optionally intercalated, together with the nitrogen atom to which they are bound, through a nitrogen atom to form a five or six-membered, saturated or unsaturated, hetero ring; it being possible for said hetero ring to be substituted with an amino group optionally substituted with a lower alkyl group; a lower alkyl group optionally substituted with a hydroxyl group; or an aminocarbonyl group optionally substituted with a lower alkyl group;

n denotes the integer 0, 1, or 2;

R^2 denotes a phenyl group optionally comprising one to three groups selected from among the group consisting of: a pyrrolyl group optionally substituted with a lower alkyl group; thienyl group; pyridylthio lower alkyl group; lower alkoxy group optionally substituted with a halogen atom on the phenyl ring; lower alkyl group, hydroxyl group, halogen atom, or the group $-O-Y-N<^{R^8}_{R^9}$ (wherein Y denotes a lower alkylene group, each of R^8 and R^9, which may be identical or different, denotes a hydrogen atom, lower alkyl group, or cycloalkyl group; and R^8 and R^9 may be optionally intercalated, with the nitrogen atom to which they are bound, through a nitrogen atom to form a five or six-membered saturated hetero ring); or the group $-N<^{R^{10}}_{R^{11}}$ (wherein each of R^{10} and R^{11}, which may be identical or different, denotes a hydrogen atom, a lower alkyl group, or a phenyl group the phenyl ring of which is optionally substituted with a group selected from the group consisting of halogen atoms, lower alkylthio groups, and lower alkyl groups optionally substituted with halogen atoms; and R^{10} and R^{11} may be optionally intercalated, with the nitrogen atom to which they are bound, through a nitrogen atom to form a five or six-membered saturated hetero ring, it being permissible for there to be one to three groups selected from the group consisting of lower alkyl groups, phenyl lower alkoxycarbonyl groups, and the group $N<^{R^{12}}_{R^{13}}$ (wherein each of R^{12} and R^{13}, which may be identical or different, denotes a hydrogen atom, lower alkyl group, or lower alkanoyl group, it being permissible for R^{12} and R^{13} to be optionally intercalated, with the nitrogen atom to which they are bound, through a nitrogen atom to form a five or six-membered saturated hetero ring) to be present on said hetero ring)].

Detailed Description of the Present Invention

Industrial Field of Application

The present invention relates to a platelet adhesion inhibitor.

Disclosure of the Invention

The platelet adhesion inhibitor of the present invention comprises an active ingredient in the form of the benzazole compound, or a salt thereof, denoted by general formula (1) below.

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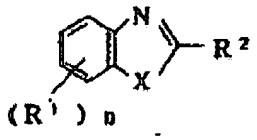
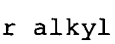
A blood platelet adhesion inhibitor characterized by comprising an active ingredient in the form of a benzazole compound, or a salt thereof, having the general formula:



[wherein X denotes a sulfur atom or the group  (wherein R^3 denotes a hydrogen atom, lower alkyl group, lower alkenyl group, or phenyl lower alkyl group);

R^1 denotes a halogen atom; cyano group; cyano-substituted lower alkoxy group; optionally halogen-substituted lower alkyl group; lower alkanoyl group; lower alkoxy group; hydroxyl group; nitro group; amino group; hydroxyl-substituted lower alkyl group; phenyl lower alkyl group optionally substituted on the phenyl ring with one to three groups selected from the group consisting of lower alkyl groups and hydroxyl groups; furyl lower alkoxy group optionally comprising a cycloalkyl group on the furyl ring; lower alkoxycarbonyl lower alkoxy group; aminothiocarbonyloxy group optionally substituted with a lower alkyl group; aminocarbonylthio group optionally substituted with a lower alkyl group; phenyl lower alkoxy group optionally substituted on the phenyl ring with one to three members selected from the group consisting of halogen atoms, lower alkyl groups, and hydroxyl groups; pyrrolidinyl lower alkyl group optionally comprising a substituent on the pyrrolidinyl ring in the form of a lower alkyl group having a hydryxol group; amidino group optionally substituted with a phenyl lower alkyl group optionally substituted on the phenyl ring with a halogen atom; amidino lower alkoxy group optionally substituted with a lower alkyl; or  (wherein A denotes a lower alkyl group; m denotes 0 or 1; each of R^4 and R^5, which may be identical or different, denotes a hydrogen atom; phenyl lower alkyl group optionally substituted on the phenyl ring with a halogen atom; lower alkanoyl group optionally substituted with a halogen atom; lower alkyl group optionally substituted with a hydroxyl group or halogen atom; cycloalkyl group; or the group (wherein l denotes 0 or 1; B denotes a lower alkylene group; each of R^6 and R^7, which may be identical or different, denotes a hydrogen atom or lower alkyl group; and R^6 and R^7 may be optionally intercalated, together with the nitrogen atom to which they are bound, through a nitrogen atom to form a five or six-membered saturated hetero ring, there optionally being on said hetero ring a substituent in the form of an amino group substituted with a lower alkyl group); and R^4 and R^5 may be optionally intercalated, together with the nitrogen atom to which they are bound, through a nitrogen atom to form a five or six-membered, saturated or unsaturated, hetero ring; it being possible for said hetero ring to be substituted with an amino group optionally substituted with a lower alkyl group; a lower alkyl group optionally substituted with a hydroxyl group; or an aminocarbonyl group optionally substituted with a lower alkyl group;

n denotes the integer 0, 1, or 2;

R^2 denotes a phenyl group optionally comprising one to three groups selected from among the group consisting of: a pyrrolyl group optionally substituted with a lower alkyl group; thienyl group; pyridylthio lower alkyl group; lower alkoxy group optionally substituted with a halogen atom on the phenyl ring; lower alkyl group, hydroxyl group, halogen atom, or the group (wherein

Y denotes a lower alkylene group, each of R^8 and R^9, which may be identical or different, denotes a hydrogen atom, lower alkyl group, or cycloalkyl group; and R^8 and R^9 may be optionally intercalated, with the nitrogen atom to which they are bound, through a nitrogen atom to form a five or six-membered saturated hetero ring); or the group $-N<^{R^{10}}_{R^{11}}$ (wherein each of R^{10} and R^{11}, which may be identical or different, denotes a hydrogen atom, a lower alkyl group, or a phenyl group the phenyl ring of which is optionally substituted with a group selected from the group consisting of halogen atoms, lower alkylthio groups, and lower alkyl groups optionally substituted with halogen atoms; and R^{10} and R^{11} may be optionally intercalated, with the nitrogen atom to which they are bound, through a nitrogen atom to form a five or six-membered saturated hetero ring, it being permissible for there to be one to three groups selected from the group consisting of lower alkyl groups, phenyl lower alkoxycarbonyl groups, and the group $N<^{R^{12}}_{R^{13}}$ (wherein each of R^{12} and R^{13}, which may be identical or different, denotes a hydrogen atom, lower alkyl group, or lower alkanoyl group, it being permissible for R^{12} and R^{13} to be optionally intercalated, with the nitrogen atom to which they are bound, through a nitrogen atom to form a five or six-membered saturated hetero ring) to be present on said hetero ring)].

The benzazole compound, or a salt thereof, denoted by general formula (1) above, has the effect of inhibiting the adhesion of blood platelets. For example, it can be used as a treatment and preventive drug for arteriosclerosis, ischemic cardiopathy, chronic arterial occlusion, acute and chronic nephritis, and the like, as well as during artificial dialysis and the implantation of artificial organs.

The various groups denoted in general formula (1) above are as follows.

Examples of lower alkyl groups are linear and branched chain alkyl groups having 1 to 6 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, pentyl, and hexyl groups.

Examples of lower alkenyl groups are linear and branched chain alkenyl groups having 2 to 6 carbon atoms, such as vinyl, allyl, 2-butenyl, 3-butenyl, 1-methylallyl, 2-pentenyl, and 2-hexenyl groups.

Examples of phenyl lower alkyl groups are phenylalkyl groups the alkyl moieties of which are straight or branched chain alkyl groups having 1 to 6 carbon atoms, such as benzyl, 2-phenylethyl, 1-phenylethyl, 3-phenylpropyl, 4-phenylbutyl, 1,1-dimethyl-2-phenylhexyl, 5-phenylpentyl, 6-phenylhexyl, and 2-methyl-3-phenylpropyl groups.

Examples of halogen atoms are fluorine, chlorine, bromine, and iodine.

Examples of lower alkyl groups optionally substituted with halogen atoms are, in addition to the above-listed lower alkyl groups, straight and branched chain alkyl groups having 1 to 6 carbon atoms comprising 1 to 3 halogen atoms as substituents, such as chloromethyl, bromomethyl, iodomethyl, trifluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 3-chloropropyl, 4-chlorobutyl, 3,4-dichlorobutyl, 3-fluoropentyl, 2,3,4-trifluoropentyl, 2,3-dichloronhexyl, and 6,6-dibromohexyl groups.

Examples of lower alkoxy groups are alkoxy groups having branched chains with 1 to 6 carbon atoms, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentyloxy, and hexyloxy groups.

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Examples of lower alkyl groups substituted with hydroxyl groups are straight and branched chain alkyl groups having 1 to 6 carbon atoms that are substituted with hydroxyl groups, such as hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl, 3-hydroxypropyl, 4-hydroxybutyl, 1,1-dimethyl-2-hydroxyethyl, 5-hydroxypentyl, 6-hydroxyhexyl, and 2-methyl-3-hydroxypropyl groups.

Examples of phenyl lower alkyl groups optionally comprising one to three groups selected from among lower alkyl groups and hydroxyl groups as substituents are, in addition to the above-described phenyl lower alkyl groups, phenyl alkyl groups optionally having one to three groups selected from the group consisting of hydroxyl groups and straight and branched chain alkyl groups having 1 to 6 carbon atoms on the phenyl ring, in which the alkyl moiety is a straight or branched chain alkyl group having 1 to 6 carbon atoms, such as 3-methylbenzyl, 2-(3,4-dimethylphenyl)ethyl, 1-(4-ethylphenyl)ethyl, 3-(2-propylphenyl)propyl, 4-(3-butylphenyl)butyl, 1,1-dimethyl-2-(4-pentylphenyl)ethyl, 5-(4-hexylphenyl)pentyl, 6-(3,4,5-trimethylphenyl)hexyl, 2-methyl-3-(2,5-dimethylphenyl)propyl, 3-hydroxybenzyl, 2-(3,4-dihydroxyphenyl)ethyl, 1-(4-hydroxyphenyl)ethyl, 3-(2-hydroxyphenyl)propyl, 4-(3-hydroxyphenyl)butyl, 1,1-dimethyl-2-(4-hydroxyphenyl)ethyl, 5-(4-hydroxyphenyl)pentyl, 6-(3,4,5-trihydroxyphenyl)hexyl, 2-methyl-3-(2,5-dihydroxyphenyl)propyl, 4-hydroxy-3,5-di-t-butylbenzyl, and 4-hydroxy-3-t-butylbenzyl groups.

Examples of furyl lower alkoxy groups optionally comprising cycloalkyl groups on the furyl ring are furyl alkoxy groups optionally comprising cycloalkyl groups having 3 to 8 carbon atoms on the furyl ring, with the alkoxy moiety being a straight or branched chain alkoxy group having 1 to 6 carbon atoms, such as (2-furyl)methoxy, 2-(3-furyl)ethoxy, 1-(2-furyl)ethoxy, 3-(3-furyl)propoxy, 4-(2-furyl)butoxy, 1,1-dimethyl-2-(3-furyl)ethoxy, 5-(2-furyl)pentyloxy, 6-(3-furyl)hexyloxy, 5-cyclopropyl-2-furyl)methoxy, 2-(2-cyclobutyl-3-furyl)ethoxy, 1-(4-cyclopentyl-2-furyl)ethoxy, 3-(5-cyclohexyl-2-furyl)propoxy, 4-(5-cycloheptyl-2-furyl)butoxy, 1,1-dimethyl-2-(4-cyclooctyl-3-furyl)ethoxy, 5-(3-cyclohexyl-2-furyl)pentyloxy, and 6-(5-cyclohexyl-3-furyl)hexyloxy groups.

Examples of lower alkoxycarbonyl lower alkoxy groups are straight and branched chain alkoxycarbonyl alkoxy groups having 1 to 6 carbon atoms in which the alkoxy moiety is a straight or branched chain alkoxy group having 1 to 6 carbon atoms, such as methoxycarbonyl methoxy, 3-methoxycarbonyl butoxy, 4-ethoxycarbonyl butoyx, 6-propoxycarbonylhexyloxy, 5-isopropoxycarbonylpentyloxy, 1,1-dimethyl-2-butoxycarbonyl ethoxy, 2-methyl-tert-butoxycarbonyl butoxy, 2-pentyloxycarbonyl ethoxy, and hexyloxycarbonyl methoxy groups.

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Examples of aminothiocarbonyloxy groups optionally substituted with lower alkyl groups are aminothiocarbonyloxy groups optionally substituted with one or two straight or branched chain alkyl groups having 1 to 6 carbon atoms, such as aminothiocarbonyloxy, methylaminothiocarbonyloxy, ethylaminothiocarbonyloxy, propylaminothiocarbonyloxy, tert-butylaminothiocarbonyloxy,

pentylaminothiocarbonyloxy, hexylaminothiocarbonyloxy, dimethylaminothiocarbonyloxy, diethylaminothiocarbonyloxy, di-n-propylaminothiocarbonyloxy, di-n-butylaminothiocarbonyloxy, dipentylaminothiocarbonyloxy, dihexylaminothiocarbonyloxy, N-methyl-N-n-butylaminothiocarbonyloxy, N-methyl-N-pentylaminothiocarbonyloxy, and N-ethyl-N-hexylaminothiocarbonyloxy groups.

Examples of aminocarbonylthio groups optionally substituted with lower alkyl groups are aminocarbonylthio groups having one or two substituents in the form of straight or branched chain alkyl groups having 1 to 6 carbon atoms, such as aminocarbonylthio, methylaminocarbonylthio, ethylaminocarbonylthio, propylaminocarbonylthio, tert-butylaminocarbonylthio, pentylaminocarbonylthio, hexylaminocarbonylthio, dimethylaminocarbonylthio, diethylaminocarbonylthio, di-n-propylaminocarbonylthio, di-n-butylaminocarbonylthio, dipentylaminocarbonylthio, dihexylaminocarbonylthio, N-methyl-N-n-butylaminocarbonylthio, N-methyl-N-pentylaminocarbonylthio, and N-ethyl-N-hexylaminocarbonylthio groups.

Examples of phenyl lower alkoxy groups optionally substituted on the phenyl ring with one to three groups selected from among the group consisting of halogen atoms, lower alkyl groups, and hydroxyl groups are phenylalkoxy groups optionally substituted on the phenyl ring with one to three members selected from among the group consisting of halogen atoms, straight and branched chain alkyl groups having 1 to 6 carbon atoms, and hydroxyl groups, in which the alkoxy moiety is a straight or branched chain alkoxy group having 1 to 6 carbon atoms, such as 2-chlorobenzyloxy, 2-(3-chlorophenylethoxy, 1-(4-chlorophenyl)ethoxy, 3-(2-fluorophenyl)propoxy, 4-(3-bromophenyl)butoxy, 1,1-dimethyl-2-(4-iodophenyl)ethoxy, 5-(2,6-dichlorophenyl)pentyloxy, 6-(3,4,5-trichlorophenyl)hexyloxy, 2-methyl-3-(3,4-difluorophenyl)butoxy, 3-methylbenzyloxy, 2-(3-4-dimethylphenyl)ethoxy, 1-(4-ethoxyphenyl)ethoxy, 3-(2-propylphenyl)propoxy, 4-(3-butylphenyl)butoxy, 1,1-dimethyl-2-(4-pentylphenyl)ethoxy, 5-(4-hexylphenyl)pentyloxy, 6-(3,4,5-trimethylphenyl)hexyloxy, 2-methyl-3-(2,5-dimethylphenyl)propoxy, 3-hydroxybenzyloxy, 2-(3,4-dihydroxyphenyl)ethoxy, 1-(4-hydroxyphenyl)ethoxy, 3-(2-hydroxyphenyl)propoxy, 4-(3-hydroxyphenyl)butoxy, 1,1-dimethyl-2-(4-hydroxyphenyl)ethoxy, 5-(4-hydroxyphenyl)pentyloxy, 6-(3,4,5-trihydroxyphenyl)hexyloxy, 2-methyl-3-(2,5-dihyroxyphenyl)propoxy, benzyloxy, 2-phenylethoxy, 1-phenylethoxy, 3-phenylpropoxy, 4-phenylbutoxy, 1,1-dimethyl-2-phenylethoxy, 5-phenylpentyloxy, 6-phenylhexyloxy, 2-methyl-3-phenylpropoxy, 4-butoxy-3,5-di-t-butylbenzyloxy, 2-chloro-4-hydroxybenzyloxy, and 4-hydroxy-3-t-butylbenzyloxy groups.

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Examples of pyrrolidinyl lower alkyl groups optionally substituted on the pyrrolidinyl ring with lower alkyl groups comprising hydroxyl groups are pyrrolidinyl alkyl groups optionally substituted on the pyrrolidinyl ring with straight or branched chain alkyl groups having 1 to 6 carbon atoms and having hydroxyl groups, in which the alkyl moiety is a straight or branched chain alkyl group having 1 to 6 carbon atoms, such as (1-pyrrolidinyl)methyl, 2-(2-pyrrolidinyl)ethyl, 1-(3-pyrrolidinyl)ethyl, 3-(1-pyrrolidinyl)propyl, 4-(2-pyrrolidinyl)butyl, 1,1-dimethyl-2-(3-pyrrolidinyl)ethyl, 5-(1-pyrrolidinyl)pentyl, 6-(2-pyrrolidinyl)hexyl, 2-methyl-3-(3-pyrrolidinyl)propyl, (2-hydroxymethyl-1-pyrrolidinyl)methyl, 2-[3-(2-hydroxyethyl)-2-pyrodinyl]ethyl, 1-[2-(1-hydroxyethyl)-3-pyrrolidinyl]ethyl, 3-[2-(3-hydroxypropyl)-1-pyrrolidinyl]propyl, 4-[1-(4-hydroxybutyl)-2-[4-(5-hydroxypentyl)-3-pyrrolidinyl]ethyl, 5-[3-(6-hydroxyhexyl)-1-pyroldinyl]pentyl, 6-[5-(2-methyl-3-hydroxypropyl)-2-

pyrrolidinyl]hexyl, and 2-methyl-3-[4-(1,1-dimethyl-2-hydroxyethyl)-3-pyrrolidinyl]propyl groups.

Examples of amidino groups optionally substituted with phenyl lower alkyl groups optionally substituted on the phenyl ring with halogens are amidino groups optionally having one to three phenyl alkyl groups in which the alkyl moiety is a straight or branched chain alkyl group having 1 to 6 carbon atoms, such as: amidino, N^1-benzylamidino, N^2-(2-phenylethyl)amidino, N^1-(1-phenylethyl)amidino, N^2-(4-phenylbutyl)amidino, N^1-(1,1-dimethyl-2-phenylethyl)amidino, N^2-(5-phenylpentyl)amidino, N^1-(6-phenylhexyl)amidino, N^2-(2-methyl-3-phenylpropyl)amidino, N^1,N^1-dibenzylamidino, N^1,N^1,N^2-tribenzylamidino, N^1-(2-chlorobenzyl)amidino, N^2-[2-(3-chlorophenyl)ethyl]amidino, N^1-[1-(4-chlorophenyl)ethyl]amidino, N^2-[3-(2-fluorophenyl)propyl]amidino, N^1-[4-(3-bromophenyl)butyl]amidino, N^2-[1,1-dimethyl-2-(4-iodophenyl)ethyl]amidon, N^1-[5-(2,6-dichlorophenyl)pentyl]amidino, N^2-[6-(3,4,5-trichlorophenyl)hexyl]amidino, and N^1-(2-chlorbenzyl)-N^2-(2-phenylethyl)amidino groups.

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Examples of amidino lower alkoxy groups optionally substituted with lower alkyl groups are amidino alkoxy groups optionally substituted with one to three straight or branched chain alkyl groups having 1 to 6 carbon atoms in which the alkoxy moiety is a straight or branched alkoxy group having 1 to 6 carbon atoms, such as amidinomethoxy, 2-amidinoethoxy, 1-amidinoethoxy, 3-amidinopropoxy, 4-amidinobutoxy, 1,1-dimethyl-2-amidinoethoxy, 5-amidinopentyloxy, 6-amidinohexyloxy, 2-methyl-3-amidinopropoxy, N^1-methylami[di]nomethoxy, 2-(N^2-ethylamidion)ethoxy, 1-(N^1-propylamidino)ethoxy, 3-(N^2-butylamidino)propoxy, 4-(N^1-pentylamidino)butoxy, 1,1-dimethyl-2-(N^2-hexylamidion)ethoxy, 5-(N^1-isopropylamidino)pentyloxy, 6-(N^2-t-butylamidino)hexyloxy, 2-methyl-3-(N^1,N^1-dimethylamidino)propoxy, N^1,N^1-dimethylamidinopropoxy, (N^1,N^1,N^2-trimethylamidino)methoxy, 2-(N^1-methyl-N^2-ethylamidino)ethoxy, 3-(N^1-methyl-N^2-propylamidino)propoxy, and 3-(N^1,N^1-dimethyl-N^2-ethylamidino)propoxy groups.

Examples of lower alkylene groups are straight and branched alkylene groups having 1 to 6 carbon atoms, such as methylene, ethylene, trimethylene, 2-methyltrimethylene, 2,2-dimethyltrimethylene, 1-methyltrimethylene, methyl methylene, ethyl methylene, tetramethylene, pentamethylene, and hexamethylene groups.

Examples of phenyl lower alkyl groups optionally substituted on the phenyl ring with halogen atoms are, in addition to the above-listed phenyl lower alkyl groups, phenyl alkyl groups, optionally substituted on the phenyl ring with 1 to 3 halogen atoms, in which the alkyl group portion consists of straight or branched chain alkyl groups having 1 to 6 carbon atoms, such as 2-chlorobenzyl, 2-(3-chlorophenyl)ethyl, 1-(4-chlorophenyl)ethyl, 3-(2-fluorophenyl)propyl, 4-(3-bromophenyl)butyl, 1,1-dimethyl-2-(4-iodophenyl)ethyl, 5-(2,6-dichlorophenyl)pentyl, 6-(3,4,5-trichlorophenyl)hexyl, 2-methyl-3-(3,4-difluorophenyl)propyl, 3,5-dichlorobenzyl, 3,4-dichlorobenzyl, and 3,5-dibromobenzyl groups.

Examples of lower alkanoyl groups are straight or branched chain alkanoyls having 1 to 6 carbon atoms, such as formyl, acetyl, propionyl, butyryl, isobutyryl, pentanoyl, and hexanoyl groups.

Examples of lower alkyl groups having substituents in the form of hydroxyls or halogen atoms are the above-listed lower alkyl groups optionally substituted with halogen atoms and lower alkyl groups substituted with hydroxyl groups.

Examples of cycloalkyl groups are cycloalkyl groups having 3 to 8 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl groups.

Examples of amino groups optionally substituted with lower alkyl groups are amino groups optionally substituted with 1 or 2 straight or branched chain alkyl groups having 1 to 6 carbon atoms, such as amino, methylamino, ethylamino, propylamino, isopropylamino, butylamino, tert-butylamino, pentylamino, hexylamino, dimethylamino, diethylamino, dipropylamino, dibutylamino, dipentylamino, dihexylamino, N-methyl-N-ethylamino, N-ethyl-N-propylamino, N-methyl-N-butylamino, and N-methyl-N-hexylamino groups. Examples of five or six-membered saturated hetero rings formed by R^6 and R^7 together with the nitrogen atom to which they are bonded and optionally intercalated through a nitrogen atom are piperazinyl, piperidinyl, and pyrrolidinyl groups.

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Examples of the above hetero rings substituted with amino groups optionally substituted with lower alkyl groups are the above-listed hetero rings substituted with amino groups optionally substituted with one or two straight or branched chain alkyl groups having 1 to 6 carbon atoms, such as 4-dimethylamino-1-piperidinyl, 2-amino-1-piperidinyl, 3-methylamino-1-piperidinyl, 4-ethylamino-1-piperidinyl, 2-propylamino-1-piperidinyl, 3-butylamino-1-piperidinyl, 4-pentylamino-1-piperidinyl, 3-hexylamino-1-piperidinyl, 4-diethylamino-1-piperidinyl, 4-(N-methyl-N-hexylamino)-1-piperidinyl, 3-amino-1-piperazinyl, 2-isopropylamino-1-piperazinyl, 3-tert-butylamino-1-piperazinyl, 2-dipropylamino-1-piperazinyl, 3-(N-methyl-N-ethylamino)-1-piperazinyl, 2-amino-1-pyrrolidinyl, 3-methylamino-1-pyrrolidinyl, 2-dihexylamino-1-pyrrolidinyl, and 3-(N-methyl-N-butylamino)-1-pyrrolidinyl groups.

Examples of five or six-membered saturated or unsaturated hetero rings formed by R^4 and R^5 together with the nitrogen atom to which they are bonded and optionally intercalated through a nitrogen atom are piperazinyl, piperidinyl, pyrrolidinyl, pyrrolyl, imidazolyl, imidazolidinyl, 2-imidazolinyl, 2-pyrrolinyl, pyrazolyl, 2-pyrazolinyl, and pyrazolidinyl groups.

Examples of aminocarbonyl groups optionally substituted with lower alkyl groups are aminocarbonyl groups optionally substitutes with 1 or 2 straight or branched chain alkyl groups having 1 to 6 carbon atoms, such as aminocarbonyl, methylaminocarbonyl, ethylaminocarbonyl, propylaminocarbonyl, isopropylaminocarbonyl, butylaminocarbonyl, tert-butylaminocarbonyl, pentylaminocarbonyl, hexylaminocarbonyl, dimethylaminocarbonyl, diethylaminocarbonyl, dipropylaminocarbonyl, dibutylaminocarbonyl, dipentylaminocarbonyl, dihexylaminocarbonyl, N-methyl-N-ethylaminocarbonyl, N-ethyl-N-propylaminocarbonyl, N-methyl-N-butylaminocarbonyl, and N-methyl-N-hexylaminocarbonyl groups.

Examples of the above hetero ring formed by R^4 and R^5 substituted with an amino group optionally substituted with a lower alkyl group, a lower alkyl group substituted with a hydroxyl group, or an aminocarbonyl group optionally substituted with a lower alkyl group are the above-described hetero rings substituted with an

amino group optionally substituted with one or two straight or branched chain alkyl group having 1 to 6 carbon atoms, a straight or branched chain alkyl group having 1 to 6 carbon atoms substituted with a hydroxyl group, or an aminocarbonyl group optionally substituted with one or two straight or branched chain alkyl groups having 1 to 6 carbon atoms, such as 4-dimethylamino-1-piperidinyl, 2-amino-1-piperidinyl, 3-methylamino-1-piperidinyl, 4-ethylamino-1-piperidinyl, 2-propylamino-1-piperidinyl, 3-butylamino-1-piperidinyl, 4-pentylamino-1-piperidinyl, 3-hexylamino-1-piperidinyl, 4-diethylamino-1-piperidinyl, 4-(N-methyl-N-hexylamino)-1-piperidinyl, 3-amino-1-piperazinyl, 2-isopropylamino-1-piperazinyl, 3-tert-butylamino-1-piperazinyl, 2-dipropylamino-1-piperazinyl, 3-(N-methyl-N-ethylamino)-1-piperazinyl, 2-amino-1-pyrrolidinyl, 3-methylamino-

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1-pyrrolidinyl,2-dihexylamino-1-pyrrolidinyl, 3-(N-methyl-N-butylamino)-1-pyrrolidinyl, 3-methylamino-1-pyrrolyl, 2-ethylamino-1-pyrrolyl, 2-propylamino-1-imidazolyl, 4-butylamino-1-imidazolidinyl, 2-pentylamino-2-imidazolinyl, 3-hexylamino-2-pyrrolinyl, 3-dimethylaminopyrazolyl, 4-diethylaminopyrazolyl, 3-dipentylamino-2-imidazolinyl, 5-dihexylamino-2-pyrrolinyl, 5-(N-methyl-N-ethylamino)pyrazolyl, 2-dimethylaminocarbonyl-1-pyrrolidinyl, 4-hydroxymethyl-1-piperazinyl, 4-hydroxymethyl-1-piperazinyl, 2-hydroxymethyl-1-pyrrolidinyl, 3-(2-hydroxyethyl)-1-piperidinyl, 3-(1-hydroxyethyl)-1-pyrrolyl, 2-(3-hydroxypropyl)-1-imidazolyl, 4-(4-hydroxybutyl)-1-imidazolidinyl, 5-(5-hydroxypentyl)-2-imidazolinine-1-yl, 2-(6-hydroxyhexyl)-2-pyrrolinine-1-yl, 3-(2-methyl-3-hydroxypropyl)pyrazolyl, 4-(1,1-dimethyl-2-hydroxyethyl)-2-pyrazolinine-1-yl, 5-hydroxymethylpyrazolidinyl, 2-(2-hydroxyethyl)-1-pyrrolidinyl, 4-aminocarbonyl-1-piperazinyl, 3-methylaminocarbonyl-1-piperazinyl, 2-ethylaminocarbonyl-1-piperazinyl, 4-isopropylaminocarbonyl-1-piperidinyl, 3-butylaminocarbonyl-1-piperidinyl, 2-pentylaminocarbonyl-1-piperidinyl, 3-hexylaminocarbonyl-1-pyrrolidinyl, 2-dimethylaminocarbonyl-1-pyrrolidinyl, 2-diethylaminocarbonyl-1-pyrrolyl, 3-dipropylaminocarbonyl-1-pyrrolyl, 2-dibutylaminocarbonyl-1-imidazolyl, 4-dipentylaminocarbonyl-1-imidazolyl, 5-dihexylaminocarbonyl-2-imidazolinyl-1-yl, 2-(N-methyl-N-ethylaminocarbonyl)-2-pyrrolinine-1-yl, 3-(N-ethyl-N-propylaminocarbonyl)-1-pyrazolinyl, 4-(N-methyl-N-butylaminocarbonyl)-2-pyrazolinine-1-yl, and 5-(N-methyl-N-hexylaminocarbonyl)-1-pyrazolindinyl groups.

Examples of pyrrolyl groups optionally substituted with lower alkyl groups are pyrrolyl groups optionally substituted with straight or branched chain alkyl groups having 1 to 6 carbon atoms, such as 2-pyrrolyl, 3-pyrrolyl, 1-pyrrolyl, 1-methyl-2-pyrrolyl, 3-ethyl-2-pyrrolyl, 2-propyl-3-pyrrolyl, 2-butyl-1-pyrrolyl, 1-pentyl-2-pyrrolyl, and 5-hexyl-3-pyrrolyl groups.

Examples of pyridylthio lower alkyl groups are pyridylthioalkyl groups in which the alkyl moiety is straight or branched chain alkyl group having 1 to 6 carbon atoms, such as (2-pyridyl)thiomethyl, 2-(3-pyridylthio)ethyl, 1-(4-pyridylthio)ethyl, 3-(2-pyridylthio)propyl, 4-(3-pyridylthio)butyl, 1,1-dimethyl-2-(4-pyridylthio)ethyl, 5-(2-pyridylthio)pentyl, 6-(3-pyridiylthio)hexyl, and 2-methyl-3-(4-pyridylthio)propyl groups.

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Examples of the five or six-membered saturated or unsaturated hetero rings formed by R^8 and R^9, R^{10} and R^{11}, and R^{12} and R^{13} with the nitrogen atom to which they

are bonded, and optionally intercalated through a nitrogen atom, are piperazinyl, piperidinyl, and pyrrolidinyl groups.

Examples of phenyl groups the phenyl ring of which is optionally substituted with one to three groups selected from the group consisting of lower alkoxy groups optionally substituted with halogen atoms, lower alkyl groups, hydroxyl groups, halogen atoms, and the group $-O-Y-N<^{R^8}_{R^9}$ (wherein R^8 and R^9 are defined as above)

are phenyl groups the phenyl ring of which is optionally substituted with one to three groups selected from the group consisting of straight or branched chain alkoxy groups having 1 to 6 carbon atoms and optionally substituted with one to three halogen atoms; straight or branched chain alkyl groups having 1 to 6 carbon atoms; hydroxyl groups; halogen atoms; and the group $-O-Y-N<^{R^8}_{R^9}$ (wherein Y denotes a straight or branched chain alkylene group having 1 to 6 carbon atoms, each of R^8 and R^9, which may be identical or different, denotes a hydrogen atom, straight or branched chain alkyl group having 1 to 6 carbon atoms, or a cycloalkyl group having 3 to 8 carbon atoms; and R^8 and R^9 may form with the nitrogen atom to which they are bound a five or six-membered saturated hetero ring that is optionally intercalated through a nitrogen atom) such as phenyl, 2-chorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-flyorophenyl, 2-bromophenyl, 3-bromophenyl, 4-bromophenyl, 2-iodophenyl, 3-iodophenyl, 4-iodophenyl, 3,5-dichlorophenyl, 2,6-dichlorophenyl, 3,4-dichlorophenyl, 3,4-difluorophenyl, 3,5-dibromophenyl, 3,4,5-trichlorophenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-ethylphenyl, 3-ethylphenyl, 4-ethylphenyl, 3-isopropylphenyl, 4-hexylphenyl, 3,4-dimethylphenyl, 2,5-dimethylphenyl, 3,4,5-trimethylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-ethoxyphenyl, 3-ethoxyphenyl, 4-ethoxyphenyl, 4-isopropyoxyphenyl, 2-propoxyphenyl, 4-hexyloxyphenyl, 3,4-dimethoxyphenyl, 3,4-diethoxyphenyl, 3,4,5-trimethoxyphenyl, 2,5-dimethoxyphenyl, 3-methyl-4-chlorophenyl, 2-chloro-6-methylphenyl, 2-methoxy-3-chlorophenyl, 2-(2-chloroethoxy)phenyl, 3-bromomethoxyphenyl, 4-trifluoromethoxyphenyl, 2-(2,2-difluoroethoxy)phenyl, 3-(3-chloropropoxy)phenyl, 4-(4-chlorobutoxy)phenyl, 2-(3-fluoropentyloxy)phenyl, 3-(6,6-dibromohexyloxy)phenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxy-3-t-butylphenyl, 4-methoxy-3-t-butylphenyl, 4-hydroxy-3,5-t-butylphenyl, 4-hydroxyphenyl, 3,4-dihydroxyphenyl, 3,4,5-trihydroxyphenyl, 2-(aminomethoxy)phenyl, 2-(2-aminoethoxy)phenyl, 4-(1-aminoethoxy)phenyl, 2,4-di(aminomethyl)phenyl, 3-(3-methylaminopropoxy)phenyl, 3-(4-methylaminobutoxy)phenyl, 4-(5-methylaminopentyloxy)phenyl, 2-(6-ethylaminohexyloxy)phenyl, 3-(2-ethylaminomethoxy)phenyl, 4-(2-ethylaminoethoxy)phenyl, 4-(1-isopropylaminoethoxy)phenyl, 4-(3-hexylaminopropoxy)phenyl, 3,4-bis(3-methylaminopropoxy)phenyl, 2-(2-dimethylaminoethoxy)phenyl, 2-(3-dimethylaminopropoxy)phenyl, 2-(4-dimethylaminobutoxy)phenyl, 2-(5-diethylaminopentyloxy)phenyl, 3-[1-(N-methyl-N-ethylamino)ethoxy]-

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phenyl, 4-[6-(N-methyl-N-isopropylamino)hexyloxy]phenyl, 4-[(N-isopropyl-N-hexylamino)methoxy]phenyl, 2-(2-di-n-butylaminoethoxy)phenyl, 2-(3-cyclohexylaminopropoxy)phenyl, 3-(2-cyclopentylaminoethoxy)phenyl, 4-[4-(N-methyl-N-cyclopeptylamino)butoxy]phenyl, 2-[2-(N-ethyl-N-cyclooctylamino)ethoxy]phenyl, 2-[3-(1-piperidinyl)butoxy]phenyl, 3-[2-(1-piperazinyl)ethoxy]phenyl, and 4-[4-(1-pyrrolidinyl)butoxy]phenyl groups.

Examples of lower alkylthio groups are straight and branched chain alkylthio groups having 1 to 6 carbon atoms, such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, tert-butylthio, pentylthio, and hexylthio groups.

Examples of phenyl groups the phenyl ring of which is optionally substituted with groups selected from the group consisting of halogen atoms, lower alkylthio groups, and lower alkyl groups optionally substituted with halogen atoms, such as a phenyl group the phenyl ring of which is optionally substituted with one to three substituents selected from the group consisting of straight or branched chain alkyl groups having 1 to 6 carbon atoms and optionally substituted with one to three halogen atoms; halogen atoms; and straight or branched chain alkylthio groups having 1 to 6 carbon atoms, are phenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-bromophenyl, 3-bromophenyl, 4-bromophenyl, 2-iodophenyl, 3-iodophenyl, 4-iodophenyl, 3,5-dichlorophenyl, 2,6-dichlorophenyl, 3,4-dichlorophenyl, 3,4-difluorophenyl, 3,5-dibromophenyl, 3,4,5-trichlorophenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-ethylphenyl, 3-ethylphenyl, 4-ethylphenyl, 3-isopropylphenyl, 4-hexylphenyl, 3,4-dimethylphenyl, 2,5-dimethylphenyl, 3,4,5-trimethylphenyl, 2-methylthiophenyl, 3-methylthiophenyl, 4-methylthiophenyl, 2-ethylthiophenyl, 3-ethylthiophenyl, 4-ethylthiophenyl, 4-isopropylthiophenyl, 4-hexylthiophenyl, 3,4-dimethylthiophenyl, 3,4-diethylthiophenyl, 3,4,5-trimethylthiophenyl, 2,5-dimethylthiophenyl, 3-methyl-4-chlorophenyl, 2-chloro-6-methylphenyl, 2-methylthio-3-chlorophenyl, 2-trifluoromethylphenyl, 4-trifluoromethylphenyl, 3-(3-chloropropyl)phenyl, 4-(2-fluoroethyl)phenyl, 2-(4-chlorobutyl)phenyl, 2-(iodomethyl)phenyl, 4-(2,3-dichlorohexyl)phenyl, and 3-(2,2,2-trifluoroethyl)phenyl groups.

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Examples of hetero rings formed by R^{10} and R^{11} above and having one to three groups selected from the group consisting of alkyl groups, phenyl lower alkoxycarbonyl groups, and the group $N<^{R''}_{R''}$ are the above-described hetero rings having one to three groups selected from the group consisting of straight or branched chain alkyl groups having 1 to 6 carbon atoms; phenylalkoxycarbonyl groups in which the alkoxycarbonyl moiety is a straight or branched chain alkoxycarbonyl group having 1 to 6 carbon atoms; and the group $N<^{R''}_{R''}$ (wherein each of R^{12} and R^{13}, which may be identical or different, denotes a hydrogen atom, straight or branched chain alkyl group having 1 to 6 carbon atoms, or straight or branched chain alkanoyl group having 1 to 6 carbon atoms, it being permissible for R^{12} and R^{13} to form with the nitrogen atom to which they are bound a five or six-membered saturated hetero ring that is optionally intercalated through a nitrogen atom), such as 3,5-dimethyl-1-piperazinyl, 4-ethyl-1-piperidinyl, 3,4,5-dimethyl-1-piperidinyl, 3-propyl-1-piperidinyl, 3,4,5-tri-methyl-1-piperazinyl, 4-butyl-1-piperazinyl, 2-penyl-1-pyrrolidinyl, 3-hexyl-1-pyrrolidinyl, 3-ethyl-4-propyl-1-piperazinyl, 3-propyl-5-methyl-1-piperazinyl, 4-amino-1-piperidinyl, 3-amino-1-pyrrolidinyl, 3-amino-1-piperazinyl, 4-acetylamino-1-piperidinyl, 2-propionylamino-1-pyrrolidinyl, 2-butyrylamino-1-piperazinyl, 3-pentanoylamino-1-piperidinyl, 2-hexanoylamino-1-piperidinyl, 4-(N-methyl-N-acetylamino)-1-piperidinyl, 3-methyl-4-amino-1-piperidinyl, 4-ethylamino-1-piperidinyl, 3-methylamino-1-pyperazinyl, 4-dimethylamino-1-piperidinyl, 2-propylamino-1-pyrrolidinyl, 3-butylamino-1-piperazinyl, 4-pentylamino-1-piperidinyl, 3-hexylamino-1-piperidinyl, 2-diethylamino-1-piperazinyl, 4-benzyloxycarbonyl-1-piperazinyl, 4-benzyloxycarbonyl-1-piperidinyl, 4-(N-methyl-N-propylamino)-1-piperidinyl, 3-benzyloxycarbonyl-1-

pyrrolidinyl, 3,5-dimethyl-4-benzyloxycarbonyl-1-piperazinyl, 3-(N-ethyl-N-hexylamino)-1-pyrrolidinyl, 3-methyl-4-dimethylamino-1-piperidinyl, 3-ethyl-5-(N-methyl-N-pentylamino)-1-piperazinyl, 4-(1-piperidinyl)-1-piperidinyl, 3-(1-pyrrolidinyl)-1-piperazinyl, 2-(1-piperazinyl)-1-pyrrolidinyl, and 3,5-dimethyl-4-amino-1-piperidinyl groups.

Examples of phenyl lower alkoxycarbonyl groups are phenylalkoxycarbonyl groups in which the alkoxycarbonyl moiety is a straight or branched chain alkoxycarbonyl group having 1 to 6 carbon atoms, such as 2-phenylethoxycarbonyl, 1-phenylethoxycarbonyl, 3-phenylpropyloxycarbonyl, 4-phenylbutoxycarbonyl, 1,1-dimethyl-2-phenylethoxycarbonyl, 5-phenylpentyloxycarbonyl, 6-phenylhexyloxycarbonyl, and 2-methyl-3-phenylpropoxycarbonyl groups.

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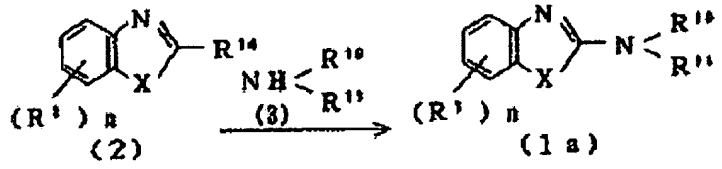
Examples of cyano-substituted lower alkoxy groups are cyanoalkoxy groups in which the alkoxy moiety is a straight or branched chain alkoxy group having 1 to 6 carbon atoms, such as cyanomethoxy, 2-cyanoethoxy, 1-cyanoethoxy, 3-cyanopropoxy, 4-cyanobutoxy, 1,1-dimethyl-2-cyanoethoxy, 5-cyanopentyloxy, 6-cyanohexyloxy, and 2-methyl-3-cyanopropoxy groups.

Examples of lower alkoxy groups substituted with halogen atoms, in addition to the above-described lower alkyl groups, are straight and branched chain alkoxy groups having 1 to 6 carbon atoms and optionally substituted with one to three halogen atoms, such as chloromethoxy, bromomethoxy, iodomethoxy, trifluoromethoxy, 2-fluoroethoxy, 2-chloroethoxy, 2,2-difluoroethoxy, 2,2,2-trifluoroethoxy, 3-chloropropoxy, 4-chlorobutoxy, 3,4-dichlorobutoxy, 3-fluoropentyloxy, 2,3,4-trifluoropentyloxy, 2,3-dichlorohexyloxy, and 6,6-dibromohexyloxy groups.

Examples of lower alkanoyl groups optionally substituted with halogen atoms, in addition to the above-described lower alkanoyl groups, are straight or branched chain alkanoyl groups having 2 to 6 carbon atoms and optionally substituted with one to three halogen atoms, such as 2-chloroacetyl, 2-bromoacetyl, 2-iodoacetyl, 2,2,2-trifluoroacetyl, 3-fluoropropanoyl, 3-chloropropanoyl, 3,3-difluoropropanoyl, 3,3,3-trifluoropropanoyl, 4-chlorobutyryl, 5-chloropentanoyl, 4,5-dichloropentanoyl, 3-fluoropentanoyl, 2,3,4-trifluoropentanoyl, 2,3-dichlorohexanoyl, and 6,6-dibromohexanoyl groups.

The above-described benzazole derivative denoted by general formula (1) can be manufactured by various methods. However, as a desirable example, it can be manufactured by the method indicated by the following reaction equation:

[Reaction Equation 1]



(wherein R^1, R^{10}, R^{11}, X, and n are defined as above and R^{14} denotes a halogen atom.)

The reaction of compounds (2) and (3) is conducted in the presence or absence of a basic compound in a suitable solvent. Specific examples of the solvent employed here are methylene chloride, chloroform, dichloroethane, and other halogenated hydrocarbons; benzene, toluene, xylene, and other aromatic hydrocarbons; diethylether, tetrahydrofuran, dimethoxyethane, and other ethers; methyl acetate, ethyl acetate, and other esters; methanol, ethanol, propanol, butanol, 3-methoxy-1-butanol, ethyl cellosolve, methyl cellosolve, and other alcohols; pyridine, 2,6-lutidine, acetone, acetonitrile, N-methylpyrrolidone, N,N-dimethylformamide, dimethylsulfoxide, hexamethylphosphate triamide, and other aprotic polar solvents; and mixed solvents thereof. Examples of the basic compound employed are compounds commonly employed in the Shotten-Baumann reaction, such as organic bases such as triethylamine, trimethylamine, pyridine, dimethylaniline, N-methylmorpholine, 1,5-diazabicylco[4,3,0]nonene-5 (DBN), 1,8-diazabicyclo[5,4,0]undecene-7 (DBU), and 1,4-diazabicyclo[2,2,2]octane (DABCO); and inorganic bases such as potassium carbonate, sodium carbonate, potassium bicarbonate, sodium bicarbonate, sodium hydroxide, potassium hydroxide, sodium hydride, potassium hydride, silver carbonate, sodium methylate, sodium ethylate, and other alcoholates.

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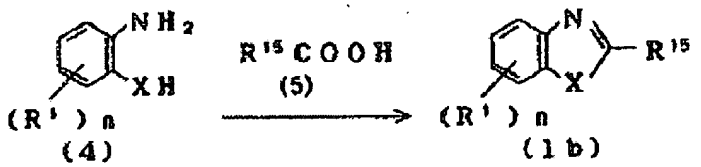
The use ratio of compounds (2) and (3) is not specifically limited and may be suitably selected over a wide range. However, the former is normally employed in at least roughly molar equivalence with the latter, preferably from molar equivalence to 20 times molar equivalence. The reaction is normally conducted from 0 to about 180°C, suitably at from room temperature to about 150°C, and generally ends in about 5 minutes to 30 hours.

[Reaction Equation 2]



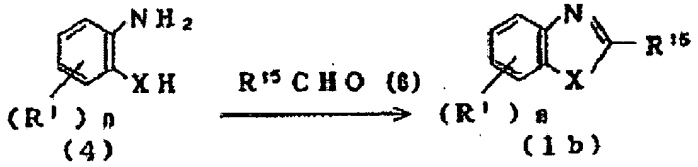
(In the equation, R_1, X, and n are defined as above. R^{15} denotes a pyridylthio lower alkyl, thienyl group, or pyrrolyl group optionally substituted with a lower alkyl group; or a phenyl group the phenyl ring of which is optionally substituted with one to three groups selected from the group consisting of lower alkoxy groups optionally substituted with halogen atoms, lower alkyl group, hydroxyl groups, halogen atoms, and the group or the group $-O-Y-N<^{R^8}_{R^9}$ (wherein Y, R^8, and R^9 are defined as above).

The reaction between compounds (4) and (5) is conducted in the presence of a condensing agent either without solvent or in a suitable solvent. Examples of the condensing agent employed here are: phosphorus oxychloride, phosphorus pentachloride, phosphorus trichloride, thionyl chloride, concentrated sulfuric acid, hydrochloric acid, polyphosphoric acid, and phosphorus pentoxide - methanesulfonic acid. Examples of the solvent employed are methanol, ethanol, propanol, butanol, 3-methoxy-1-butanol, ethyl cellosolve, methyl cellosolve, other alcohols, benzene, toluene, xylene, other aromatic hydrocarbons, diethylether, tetrahydrofuran, dioxane, diglyme, monoglyme, other ethers, dichloromethane,

chloroform, carbon tetrachloride, other halogenated hydrocarbons, dimethylformamide (DMF), dimethylsulfoxide (DMSO), hexamethylphosphoramide (HMPA), acetonitrile, and other polar solvents.

The reaction is normally conducted at from room temperature to 150°C, preferably from room temperature to the vicinity of 100°C, for from 15 minutes to about 15 hours. The quantity of compound (5) employed is at least the molar equivalent of compound (4), preferably from molar equivalence to about 1.5 times molar equivalence.

[Reaction Equation 3]



(In the equation, R^{15}, X, and n are defined as above.)

The reaction of compounds (4) and (6) is conducted in a suitable solvent in the presence or absence of a basic compound. Examples of the basic compound employed here are sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, and other inorganic bases, and piperidine, pyridine, triethylamine, DBN, DBU, DABCO, and other organic bases. Examples of the solvent are water; methanol, ethanol, isopropanol, and other alcohols; dioxane, tetrahydrofuran, diethylether, ethyleneglycol dimethylether, and other ethers; benzene, toluene, xylene, and other aromatic hydrocarbons; dichloromethane, dichloroethane, chloroform, carbon tetrachloride, and other halogenated hydrocarbons; and pyridine, DMF, DMSO, HMPA, and other polar solvents. The quantity of compound (6) employed is at least the molar equivalent of compound (4), preferably the molar equivalent to five times the molar equivalent. The reaction is normally conducted at from 0 to 150°C, preferably from 0 to 100°C, for a reaction time of 10 minutes to about 30 hours.

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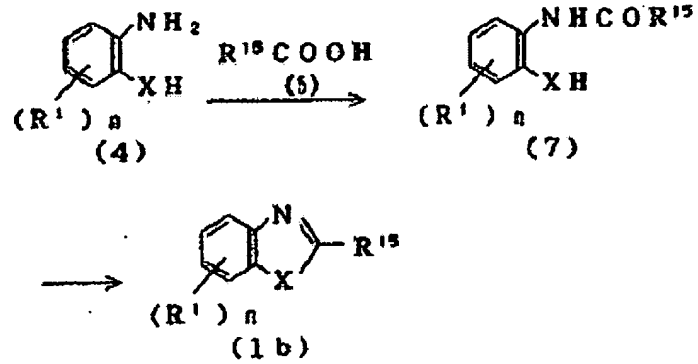
[Reaction Equation 4]



(In the equation, R^1, R^{15}, X, and n are defined as above.)

The reaction of compounds (4) and (5) is appended to the usual amido bond-generating reaction. In this case, an activated compound may be employed as carboxylic acid (5). Conditions suited to common amido bond-generating reactions may be employed for the amido bond-generating reaction. Examples are: (a) the mixed acid anhydride method, in which an alkyl halocarboxylic acid is reacted with carboxylic acid (5) to obtain a mixed acid anhydride, which is then reacted with compound (4); (b) the active ester or active amide method, in which carboxylic acid (5) is reacted, for example, with an active ester such as p-nitrophenylester, N-hydroxysuccinic acid imidoester, or 1-hydroxybenzotriazole ester, or an active amide such as benzoxazoline-2-thione, and the product is reacted with compound (4); (c) the carbodiimide method, in which compound (4) is dehydration bonded to carboxylic acid (5) in the presence of, for example, a dehydrating agent such as dicyclohexylcarbodiimide or carbonyldiimidazole; (d) the carboxylic acid halide method, in which carboxylic acid (5) is converted to a halide which is then reacted with compound (4); and (e) other methods, such as using a dehydrating agent such as acetic anhydride to convert carboxylic acid (5) to a carboxylic anhydride, which is then reacted with compound (4), and reacting compound (4) with an ester of carboxylic acid (5) with a lower alcohol, for example, under high pressure and at high temperature. It is also possible to activate carboxylic acid (5) with a phosphorus compound such as triphenylphosphine or diethylchlorophosphate and then react it with compound (4).

Examples of the alkyl halocarboxylic acid employed in the mixed acid anhydride reaction are: methyl chloroformate, methyl bromoformate, ethyl chloroformate, ethyl bromoformate, and isobutyl chloroformate. The mixed acid anhydride can be obtained by the usual Shotten-Baumann reaction and then reacted with compound (4) without the usual isolation to produce compound (7). The Shotten-Baumann reaction is normally conducted in the presence of a basic compound. The basic compound employed may be any compound that is commonly employed in the Shotten-Baumann reaction; examples are: triethylamine, trimethylamine, pyridine, dimethylaminopyridine, dimethylaniline, N-methylmorpholine, 4-dimethylaminopyridine, DBN, DBU, DABCO, and other organic bases; and potassium carbonate, sodium carbonate, potassium bicarbonate, sodium bicarbonate, and other inorganic bases. The reaction is conducted at about -20 to 100°C, preferably 0 to 50°C, for a period of about 5 minutes to 10 hours, preferably from 5 minutes to 2 hours. The reaction of the mixed acid anhydride obtained with compound (4) is conducted at about -20 to 150°C, preferably from 10 to 50°C, for about 5 minutes to 10 hours, preferably from about 5 minutes to 5 hours. The mixed acid anhydride method may be conducted without the use of a solvent, but is generally conducted in a solvent. The solvent employed may be any solvent that is generally employed in mixed acid anhydride methods; specific examples are: methylene chloride, chloroform, dichloroethane, and other halogenated hydrocarbons; benzene, toluene, xylene, and other aromatic hydrocarbons; diethylether, diisopropylether, tetrahydrofuran, dimethoxyethane, and

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other ethers; methyl acetate, ethyl acetate, and other esters; and dimethylformamide, dimethylsulfoxide, hexamethylphosphoric acid triamide, and other aprotic polar solvents. The proportions of carboxylic acid (5), alkyl halocarboxylic acid, and compound (4) employed in this method are normally at least equimolar. However, the alkyl halocarboxylic acid and compound (4) are desirably each employed in quantities of 1 to 2 moles per mole of carboxylic acid (5).

When using benzoxazoline-2-thioneamide, for example, the active ester or active amide method described in (b) above can be conducted in a suitable solvent that does not affect the reaction, such as the solvents suitable for use in the above-described mixed acid anhydride method, as well as 1-methyl-2-pyrrolidone or the like, at 0 to 150°C, preferably 10 to 100°C, for 0.5 to 75 hours. In this case, compound (4) and benzoxazoline-2-thioneamide are normally employed in at least equimolar quantities, preferably with the latter being employed in a quantity of 1 to 2 moles per mole of the former. When employing N-hydroxysuccinic acid imidoester, the reaction is advantageously conducted in the presence of a suitable base, such as the bases employed in the carboxylic acid halide method described further below.

In the carboxylic acid halide method of (c) above, carboxylic acid (5) is reacted with a halogenating agent to obtain a carboxylic acid halide. With or without having been isolated and purified, the carboxylic acid halide is then reacted with compound (4). The reaction of this carboxylic acid halide with compound (4) is conducted in a suitable solvent in the presence or absence of a dehalogenating hydrogen agent. The usual basic compounds may be employed as the dehalogenating hydrogen agent; in addition to the basic compounds employed in the above described Shotten-Baumann reaction, sodium hydroxide, potassium hydroxide, sodium hydride, potassium hydride, silver carbonate, and other inorganic bases may be employed. Compound (4) may be employed in excess to double quantity as a dehalogenating hydrogen agent. In addition to the solvents employed in the above-described Shotten-Baumann reaction, for example, water; methanol, ethanol, propanol, butanol, 3-methoxy-1-butanol, ethyl cellosolve, methyl cellosolve, and other alcohols; pyridine, acetone, acetonitrile, and the like; and mixed solvents of two or more of the above may be employed. The proportions of compound (4) and the carboxylic acid halide employed are not specifically limited and may be selected over a broad range. However, the former is normally employed in a quantity of at least 1 mole, preferably 1 to 5 moles, per mole of the latter. The reaction temperature is normally about -30 to 180°C, preferably about 0 to 150°C. The reaction normally concludes in 5 minutes to 30 hours. The carboxylic acid halide employed can be produced by reacting carboxylic acid (5) with a halogenating agent in the presence or absence of a solvent. Any solvent that does not negatively affect the reaction may be employed; examples are benzene, toluene, xylene, and other aromatic hydrocarbons; chloroform, methylene chloride, carbontetrachloride, and other halogenated hydrocarbons; dioxane, tetrahydrofuran, diethylether, and other ethers; and dimethylformamide, dimethylsulfoxide, and the like. A common halogenating agent capable of replacing the hydroxyl group of the carboxyl group with a halogen may be employed as the halogenating agent; examples are thionyl chloride, oxazolyl chloride, phosphorus oxychloride, phosphorus oxybromide, phosphorus pentachloride, and phosphorus pentabromide. The proportions of carboxylic acid (5) and halogenating agent employed are not specifically limited and may be suitably selected. However, when conducting the reaction in the absence of solvent, the latter is generally employed in a greatly excessive quantity relative to the former. When conducting the reaction in a solvent, the latter is generally employed in a quantity of at least 1 mole, preferably 2 to 4 moles, per mole of the former. Neither the reaction temperature nor the reaction time is specifically limited. However, a temperature of from room temperature to about 100°C, preferably 50 to 80°C, and a period of about from 30 minutes to 6 hours, are generally employed.

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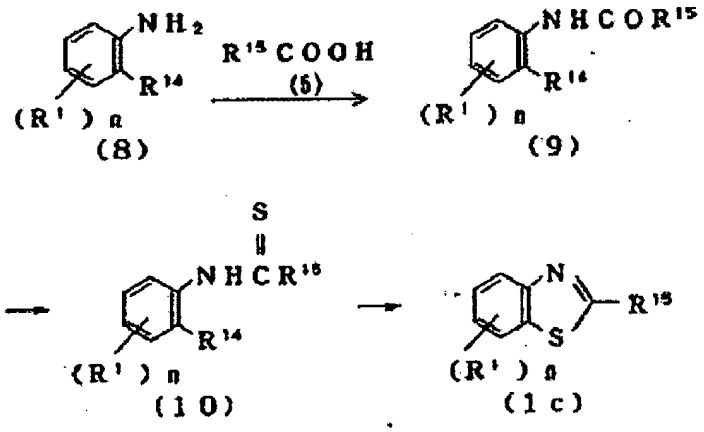
The method in which carboxylic acid (5) is activated with a phosphorus compound such as triphenylphosphine, diethylchlorophosphate, diphenylphosphinyl chloride, phenyl-N-phenylphosphoramide chloridate, diethyl cyanophosphate, and bis(2-oxo-3-oxazolidinyl)phosphinic chloride, and then reacted with compound (4) may be conducted in a suitable solvent. Any solvent that does not affect the reaction may be employed; specific examples are: methylene chloride, chloroform, dichloroethane, and other halogenated hydrocarbons; benzene, toluene, xylene, and other aromatic hydrocarbons; diethylether, tetrahydrofuran, dimethoxyethane, and other ethers; methyl acetate, ethyl acetate, and other esters; dimethylformamide, dimethylsulfoxide, hexamethylphosphoric acid triamide, and other aprotic polar solvents. In the reaction, since compound (4) functions as a basic compound, the reaction will progress well when employing compound (4) in excess of the theoretical quantity. As needed, other basic compounds may be employed, such as triethylamine, trimethylamine, pyridine, dimethylaniline, N-methylmorpholine, 4-dimethylaminopyridine, DBN, DBU, DABCO, and other organic bases; as well as potassium carbonate, sodium carbonate, potassium bicarbonate, sodium bicarbonate, and other inorganic bases. The reaction is conducted at about 0 to 150°C, preferably about 0 to 100°C, generally for about 5 minutes to 30 hours. The phosphorus compound and carboxylic acid (5) are generally employed in quantities of at least 1 mole, preferably 1 to 3 moles, per mole of compound (4).

The reaction converting compound (7) to compound (1b) may be conducted under the same conditions as the reaction between compounds (4) and (5).

[Reaction Equation 5]



(In the equation, R^1, R^{14}, R^{15}, and n are defined as above.)

The reaction between compounds (8) and (5) is conducted under the same conditions as the reaction between compounds (4) and (5) of above-described Reaction Equation 4.

The reaction converting compound (9) to compound (10) may be conducted in the absence or presence of a suitable solvent and in the presence of a sulfurizing agent such as 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetan-2,4-disulfide (Lawesson's reagent) or phosphorus pentasulfide. Examples of solvents that are suitable for use here are: methanol, ethanol, propanol, and other lower alcohols; diethylether, tetrahydrofuran, dioxane, ethylene glycol monomethylther, and other

ethers; dichloromethane, chloroform, carbontetrachloride, and other halogenated hydrocarbons; benzene, toluene, xylene, and other aromatic hydrocarbons; methyl acetate, ethyl acetate, and other esters; acetone, methyl ethyl ketone, and other ketones; acetonitrile, dimethylsulfoxide, hexamethyl phosphoric acid triamide, and other polar solvents; and mixtures of these solvents. The quantity of sulfurizing agent employed is normally 0.5 to 2 moles, preferably 0.5 to 1.5 moles, per mole of compound (9). The reaction is normally conducted at 50 to 300°C, preferably about 50 to 250°C, for a period of 1 to 15 hours.

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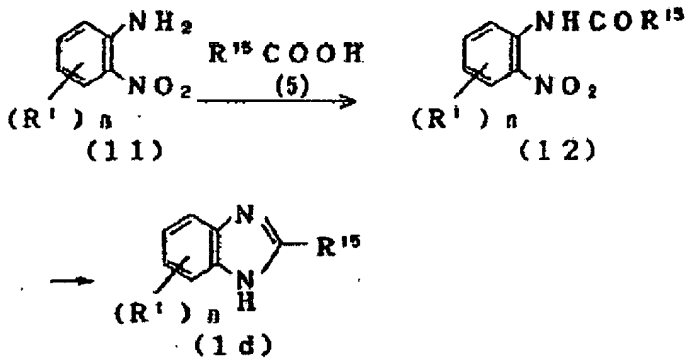
The reaction in which compound (10) is converted to compound (1c) is conducted in a suitable solvent in the presence of 1,1,3,3-tetramethylguanidine. Any of the solvents in the reaction converting compound (9) to compound (10) in above-described Reaction Equation 5 may be employed here. The quantity of 1,1,3,3-tetramethylguanidine employed is at least 1 mole to 2 moles per mole of compound (10). The reaction is normally conducted at from room temperature to 200°C, preferably from about room temperature to 150°C, for about 1 to 7 hours.



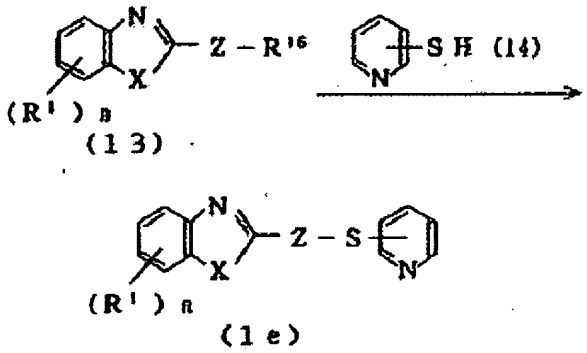
(In the equation, R^1, R^{15}, and n are defined as above.)

The reaction between compounds (11) and (5) may be conducted under the same conditions as the reaction between compounds (4) and (5) in above-described Reaction Equation 4.

The reaction deriving compound (1d) from compound (12) may be conducted in a suitably inert solvent by reduction with a reducing agent in the form of a metal; a mixture of a metal or metal salt and an acid; or a mixture of a metal or a metal salt and an alkali metal hydroxide, sulfate, or ammonium salt. The reaction may be conducted using a reducing agent in the form of a metal such as stannous chloride, iron, or zinc; a mixture of iron, zinc, tin, or stannous tin with an inorganic acid such as hydrochloric acid or sulfuric acid; or a mixture of iron, ferrous sulfate, zinc, or tin and an alkali metal hydroxide such as sodium hydroxide, a sulfide such as ammonium sulfide, ammonia water, or an ammonium salt such as ammonium chloride. Examples of the inert solvent employed are water, acetic acid, methanol, ethanol, and dioxane. The conditions of the above-described reduction reaction may be suitably selected based on the reducing agent employed. When employing stannous chloride and hydrochloric acid as the reducing agent, the reaction is advantageously conducted at a temperature of about 0 to 150°C for a period of about

0.5 to 10 hours. The reducing agent is employed in a proportion of at least 1 mole, normally 1 to 6 moles, per mole of starting material compound.

[Reaction Equation 7]



(In the equation, X and n are defined as above. Z denotes a lower alkylene group. R^{16} denotes a halogen atom, lower alkanesulfonyloxy group, arylsulfonyloxy group, or aralkylsulfonyloxy group.)

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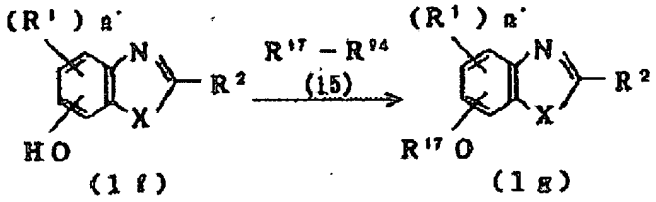
The halogen atom denoted by R^{16} is identical to those set forth above. Specific examples of lower alkanesulfonyloxy groups are: methanesulfonyloxy, ethanesulfonyloxy, isopropanesulfonyloxy, propanesulfonyloxy, butanesulfonyloxy, tert-butanesulfonyloxy, pentanesulfonyloxy, and hexanesulfonyloxy groups. Specific examples of arylsulfonyloxy groups are phenylsulfonyloxy, 4-methylphenylsulfonyloxy, 2-methylphenylsulfonyloxy, 4-nitrophenylsulfonyloxy, 4-methoxyphenylsulfonyloxy, 3-chlorophenylsulfonyloxy, α-naphthylsulfonyloxy groups, and other substituted and unsubstituted arylsulfonyloxy groups. Specific examples of aralkylsulfonyloxy groups are benzylsulfonyloxy, 2-phenylethylsulfonyloxy, 4-phenylbutylsulfonyloxy, 4-methylbenzylsulfonyloxy, 2-methylbenzylsulfonyloxy, 4-nitrobenzylsulfonyloxy, 4-methoxybenzylsulfonyloxy, 3-chlorobenzylsulfonyloxy, α-naphthylmethylsulfonyloxy groups, and other substituted and unsubstituted sulfonyloxy groups.

The reaction of compounds (13) and (14) can be conducted in a suitable solvent in the presence of a basic compound. Any solvent that does not affect the reaction may be employed. Examples are: water; methanol, ethanol, isopropanol, and other alcohols; benzene, toluene, xylene, and other aromatic hydrocarbons; diethylether, tetrahydrofuran, dioxane, monoglyme, diglyme, and other ethers; acetone and other ketones; methyl acetate, ethyl acetate, and other esters; N,N-dimethylformamide, dimethylsulfoxide, and hexamethylphosphoric acid triamide; and mixtures of these solvents. Examples of the basic compound employed are: sodium hydride, potassium hydride, sodium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, silver carbonate, and other inorganic bases; metallic sodium metallic potassium, and other alkali metals; sodium methylate, sodium ethylate, and other alcoholates; triethylamine, pyridine, N,N-dimethylaminopyridine, DBN, DBU, DABCO, and other organic bases. The reaction is normally conducted at 0 to 150°C, preferably about 0 to 100°C, for about 15 minutes to 10 hours. The quantity of compound of general formula (14) employed is

normally at least 1 mole, preferably 1 to 1.5 moles, per mole of the compound of general formula (13).

[Reaction Equation 8]



(In the equation, R^1, R^2, X, and R^{14} are defined as above. n' denotes 0 or 1. R^{17} denotes a lower alkyl group, furyl lower alkyl group having a cycloalkyl group on the furyl ring, lower alkoxy carbonyl lower alkyl group, aminothiocarbonyl group optionally substituted with a lower alkyl group, phenyl lower alkyl group substituted on the phenyl ring with 1 to 3 groups selected from the group consisting of halogen atoms, lower alkyl groups, and hydroxyl groups, or the group $-A-N<^{R^4}_{R^5}$ (wherein R^4 and R^5 are defined as above.))

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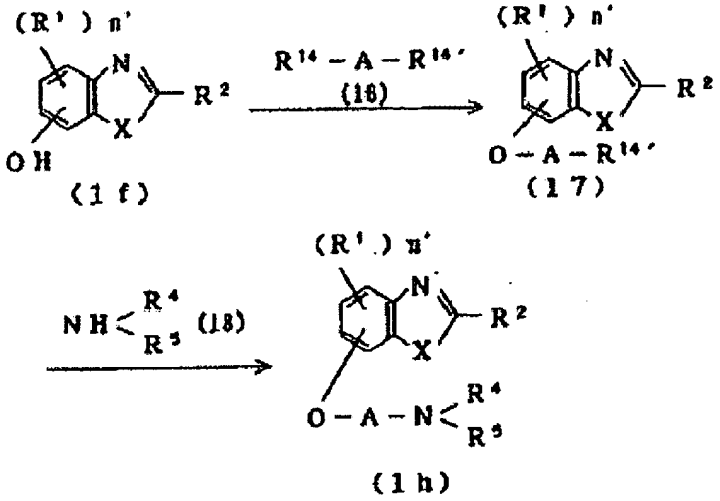
The reaction between compounds (1f) and (15) and the reaction between the compound of general formula (1f) and the compound of general formula (15) are generally conducted in a suitably inert solvent in the presence or the absence of a basic compound. Examples of the inert solvent employed are water; benzene, toluene, xylene, and other aromatic hydrocarbons; methylene chloride, chloroform, carbon tetrachloride, and other aromatic hydrocarbons; tetrahydrofuran, dioxane, diethyleneglycol dimethylether, and other ethers; methanol, ethanol, isopropanol, butanol, and other lower alcohols; acetic acid; ethyl acetate; acetone; acetonitrile; dimethyl sulfoxide; dimethyl formamide; hexamethyl phosphoric acid triamide; and mixtures of the same. Examples of basic compounds are sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, and other carbonates; sodium hydroxide, potassium hydroxide, and other metal hydroxides; sodium hydride, potassium, sodium, sodium amide, sodium methylate, sodium ethylate, and other metallic alcoholates; pyridine, ethyl-diisopropylamine, dimethylaminopyridine, triethylamine, DBN, DBU, DABCO, and other organic bases. The proportions of the compound of general formula (1f) and the compound of general formula (15) employed are not specifically limited and may be suitably selected over a broad range. However, the former is generally employed in a quantity of at least 1 mole, preferably about 1 to 10 moles, per mole of the former. The reaction is normally conducted at about 0 to 200°C, preferably about 0 to 170°C, generally for 30 minutes to about 50 hours. Sodium iodide, potassium iodide, and other alkali metal halides may be added to the reaction system of this reaction.

[Reaction Equation 9]

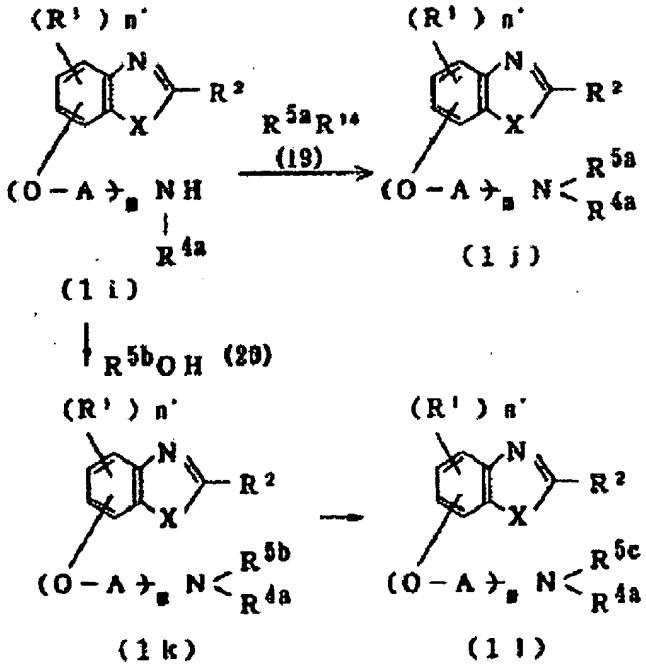


(In the equation, R^1, R^2, R^{14}, X, n', A, R^4, and R^5 are defined as above. $R^{14'}$ denotes a halogen atom.)

The reaction between compounds (1f) and (16) is conducted under the same conditions as the reaction between compounds (1f) and (15) in Reaction Equation 8.

The reaction of compounds (17) and (18) is conducted under the same conditions as the reaction between compounds (1f) and 15) of Reaction Equation 8. In the reaction, compound (18) may be employed in great excess instead of using a basic compound.

[Reaction Equation 10]



(In the equation, R^1, R^2, R^{14}, A, X, m, and n' are defined as above. R^{4a} denotes a hydrogen atom; a phenyl lower alkyl group substituted on the phenyl ring with a halogen atom; a lower alkanoyl group substituted with a halogen atom; a lower alkyl group optionally substituted with a hydroxyl group or halogen atom; a cycloalkyl group, or the group $-(C)_{\ell}-B-N<^{R^6}_{R^7}$ (wherein l, B, R^6, and R^7 are defined as above). R^{5a} denotes a phenyl lower alkyl group optionally substituted on the phenyl ring with a halogen atom; a lower alkyl group optionally substituted with a hydroxyl group or halogen atom; a cycloalkyl group; or the group $-B-N<^{R^6}_{R^7}$ (wherein R^6 and R^7 are defined as above). R^{5b} denotes a lower alkanoyl group optionally substituted with a halogen atom or the group $-COB-N<^{R^6}_{R^7}$ (wherein R^6 and R^7 are defined as above). R^{5c} denotes a lower alkyl group optionally having a halogen atom or the group $-B'-N<^{R^6}_{R^7}$ (wherein R^6 and R^7 are defined as above and B' denotes a lower alkylene group).)

The reaction of compounds (1i) and (19) is conducted under the same conditions as the reaction between compounds (1f) and (15) in above-described Reaction Equation 8.

The reaction of compounds (1i) and (20) is conducted under the same conditions as the reaction between compounds (4) and (5) in above-described Reaction Equation 4.

The reaction converting compound (1k) to compound (1i) is conducted by reducing compound (1k). This conversion reaction is conducted in a suitable solvent in the presence of a hydrogenating reducing agent. Examples of the reducing agent employed are: sodium borohydride, aluminum lithiumhydride, and diborane. The quantity of reducing agent employed is at least 1 mole, preferably 1 to 5 moles, per mole of starting material. Examples of the solvent employed are: water, dichloromethane, chloroform, carbon tetrachloride, and other halogenated hydrocarbons; methanol, ethanol, isopropanol, and other lower alcohols; tetrahydrofuran, dioxane, diethylether, diglyme, and other ethers; and mixtures of the same. The reaction is normally conducted at from -60 to 100°C, preferably from about 30 to 100°C, for a period of about 10 minutes to 5 hours. When employing aluminum lithiumhydride or diborane as the reducing agent, a solvent in the form of an anhydrous solvent such as diethylether, tetrahydrofuran, or diglyme may be employed. When employing sodium borohydride as the reducing agent, an acid such as acetic acid may be added.

When R^{5b} in the compound of general formula (1k) denotes a lower alkanoyl group optionally substituted with a halogen atom, the various compounds may be obtained by reacting an alkanoyl-producing agent such as $(R^{5b'})_2O$ (wherein $R^{5b'}$ denotes a lower alkanoyl group optionally substituted with a halogen atom) and compound (1i) in the absence of solvent or in the presence of a suitable solvent, in the presence (preferred) or absence of a basic compound.

Examples of the above-mentioned suitable solvent are the above-described aromatic hydrocarbons; methanol, ethanol, propanol, and other lower alcohols; dimethylformamide; dimethylsulfoxide; chloroform, methylene chloride, and other

halogenated hydrocarbons; acetone; and pyridine. Examples of the basic compound are triethylamine, pyridine, and other tertiary amines; sodium hydroxide; potassium hydroxide, potassium carbonate, and sodium bicarbonate. The reaction may be conducted in a solvent such as acetic acid in the presence of an inorganic acid such as sulfuric acid.

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The quantity of lower alkanoyl agent employed is desirably not less than 1 mole, preferably 1 to 10 moles, per mole of starting material. The reaction is normally conducted at from about 0 to 200°C, preferably about 0 to 150°C, for about 0.5 to 15 hours.

Compounds in which R^{5a} in general formula (1j) denotes a lower alkyl group or a phenyl lower alkyl group can be obtained by the reaction of compound (1i) and the following compound:

$$R^{29} - CO - R^{30} \qquad (40)$$

(each of wherein R^{29} and R^{30} denotes a hydrogen atom, phenyl group, or lower alkyl group).

This reaction is conducted in the absence of solvent or in a suitable solvent in the presence of a reducing agent. Examples of the solvent employed here are: water; methanol, ethanol, isopropanol, and other alcohols; formic acid; acetic acid; dioxane; diethylether, diglyme, tetrahydrofuran, and other ethers; benzene, toluene, xylene, and other aromatic hydrocarbons; and mixtures of these solvents. Examples of the reducing agent are formic acid; aliphatic alkali metal salts such as sodium formate; sodium borohydride, sodium cyanoborohydride, aluminum lithiumhydride, and other hydrogenating reducing agents; palladium - black, palladium - carbon, platinum oxide, platinum black, Raney nickel, and other catalytic reducing agents.

When employing formic acid as the reducing agent, the reaction temperature is normally from room temperature to about 200°C, preferably from about 50 to 150°C, and the reaction time is about 1 to 10 hours. The formic acid may be employed in a quantity greatly in excess of compound (1i).

When employing a hydrogenating reducing agent, the reaction temperature is normally about -30 to 100°C, preferably about 0 to 70°C, and the reaction is conducted for about 30 minutes to 12 hours. The reducing agent is normally employed in a quantity of from about 1 mole to 20 moles, preferably about 1 to 6 moles, per mole of compound (1i). In particular, when employing aluminum lithiumhydride as the reducing agent, it is desirable to employ a solvent in the form of diethylether, dioxane, tetrahydrofuran, diglyme, or some other ether; or benzene, toluene, xylene, or some other aromatic hydrocarbon.

When employing a catalytic reducing agent, the reaction is desirably conducted in a hydrogen atmosphere of from about ordinary pressure to 20 atmospheres, preferably from ordinary pressure to about 10 atmospheres; or in the presence of a hydrogen donor such as formic acid, ammonium formate, cyclohexene, or hydrazine hydrate; normally at a temperature of about -30 to 100°C, preferably about 0 to 60°C; and normally for a period of about 1 to 12 hours. The catalytic

reducing agent is normally employed in a quantity of about 0.1 to 40 weight percent, preferably about 1 to 20 weight percent, of compound (1i).

Compound (40) is normally employed in a quantity of at least 1 mole, preferably from 1 mole to a great excess, per mole of compound (1i). In this reaction, when R^{4a} in compound (1i) denotes a hydrogen atom, the reaction with compound (40) sometimes yields a compound in which R^{4a} and R^{5a} of compound (1i) both denote the group $-CH\lesssim^{R^{29}}_{R^{30}}$.

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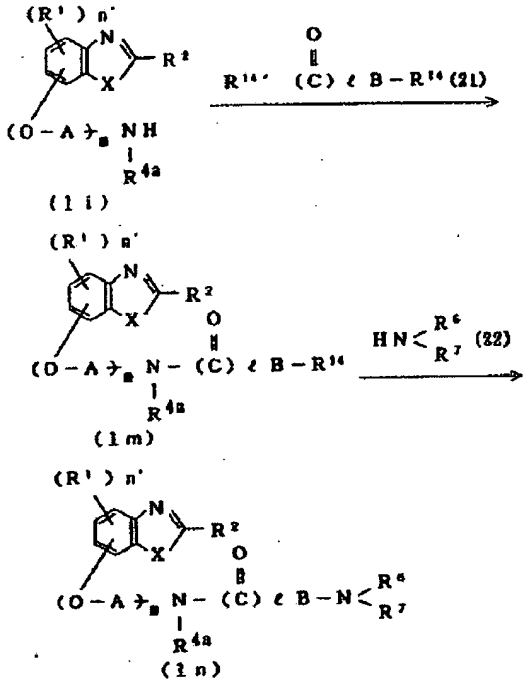
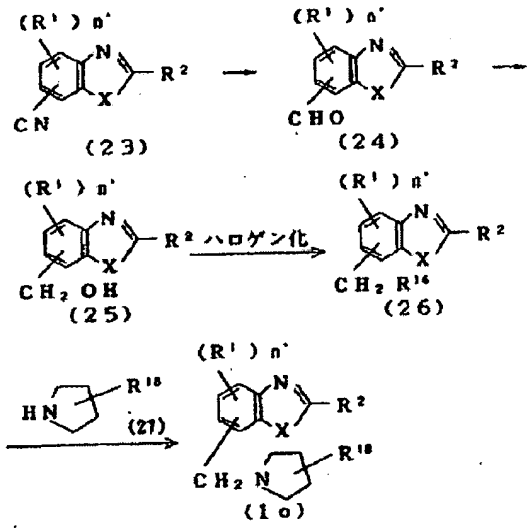
[Reaction Equation 11]



(In the equation, R^1, R^{4a}, R^{14}, $R^{14'}$, R^6, R^7, A, X, n', m, and l are all defined as above.)

The reaction between compounds (1i) and (21) and the reaction between compounds (1m) and (22) are conducted under the same conditions as the reaction between compounds (1f) and (15) of Reaction Equation 8 and the reaction between compounds (17) and (18) in Reaction Equation 9, respectively.

[Reaction Equation 12]



[(middle arrow) Halogenation]

(In the equation, R^1, R^2, R^{14}, X, and n' are defined as above. R^{18} denotes a hydrogen atom or a lower alkyl group optionally substituted with hydroxyl group.)

The reaction converting compound (23) to compound (24) is conducted by reducing compound (23). This reducing reaction is conducted in a suitable solvent in the presence of a hydrogenating reducing agent. Examples of the reducing agent employed are diisobutylaluminum hydride, sodium triethoxyaluminum hydride, lithium tri-t-butylaluminum hydride, and other alkyl aluminumhydrides; lithium aluminumhydride; sodium [2-(dimethylamino)ethoxy]aluminumhydride; and triethyloxonium tetrafluoroborate - triethylsilane hydride. Examples of the solvent employed are tetrahydrofuran, diethylether, diglyme, and other ethers; benzene, toluene, xylene, and other aromatic hydrocarbons; and dichloromethane, chloroform, carbon tetrachloride, and other halogenated hydrocarbons. The reaction is normally conducted at from -60 to 100°C, preferably from about -60 to 50°C, for about 10 minutes to 10 hours. When employing lithium aluminumhydride as reducing agent, it suffices to employ an anhydrous solvent such as diethylether, tetrahydrofuran, or diglyme. The quantity of reducing agent employed is at least 1 mole, preferably about 1 to 3 moles, per mole of compound (23).

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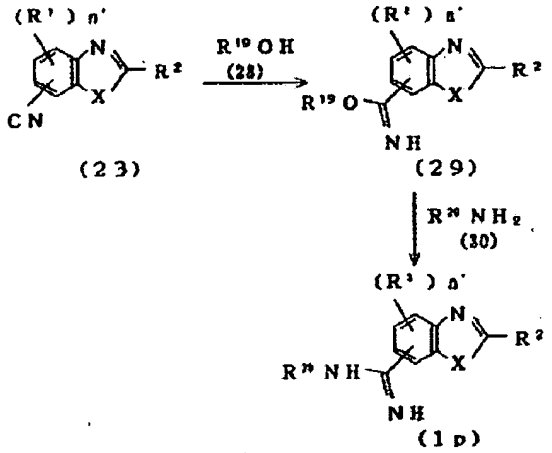
The reaction converting compound (24) to compound (25) is conducted under the same conditions as the above-described reaction converting compound (1k) of Reaction Equation 10 to compound (11).

Any reaction conditions commonly employed in the halogenation of hydroxyl groups may be employed in the halogenation reaction of compound (25). For example, it suffices to react compound (25) with a halogenating agent in a suitably inert solvent or in the absence of solvent. Examples of the halogenating agent employed are hydrochloric acid, hydrobromic acid, and other halogenated hydracids; N,N-diethyl-1,2,2-trichlorovinylamide; phosphorus pentachloride; phosphorus pentabromide; phosphorus oxychloride; and thionyl chloride. Examples of inert solvents are dioxane, tetrahydrofuran, and other ethers; and chloroform, methylene chloride, carbon tetrachloride, and other halogenated hydrocarbons. The

halogenating agent is normally employed in a proportion of at least 1 mole, preferably more than 1 mole, per mole of compound (25). The reaction is normally conducted at from 0 to 150°C, preferably 0 to 120°C, for from about 10 minutes to 15 hours.

The reaction between compounds (26) and (27) is conducted under the same conditions as the reaction between compounds (1f) and (15) of above-described Reaction Equation 8.

[Reaction Equation 13]



(In the equation, R^1, R^2, X, and n' are defined as above. R^{19} denotes a lower alkyl group, and R^{20} denotes a hydrogen atom or a phenyl lower alkyl group optionally substituted on the phenyl ring with a halogen atom.)

The reaction between compounds (23) and (28) is conducted in a suitable solvent or in the absence of solvent and in the presence of a suitable basic compound or hydrogen chloride gas. Examples of the solvent employed here are: dichloromethane, chloroform, and other halogenated hydrocarbons, as well as benzene, toluene, and other aromatic hydrocarbons.

The quantity of compound (28) employed is at least 1 mole, preferably from 1 mole to a large excess, per mole of compound (23). Examples of basic compounds are sodium methylate, sodium ethylate, and other metallic alcoholates. In particular, alcoholates identical to the alcohols employed in the above-described reaction (compound (28)) are suitably employed. The reaction temperature is desirably about -10 to 50°C, preferably 0°C to about room temperature. The reaction generally concludes in about 1 to 200 hours.

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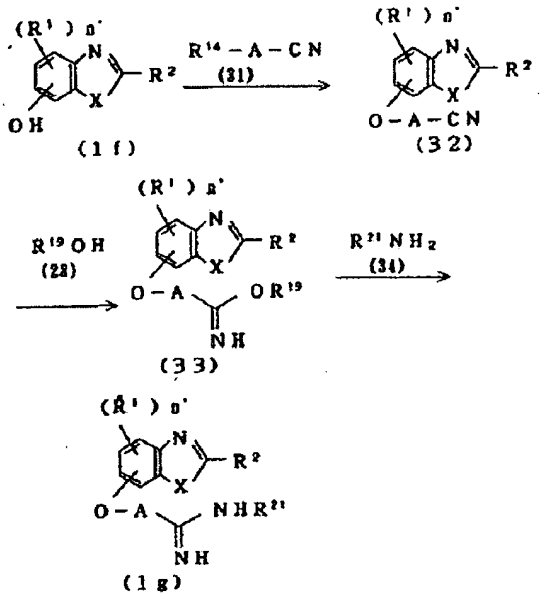
Examples of the solvent employed in the reaction between compounds (29) and 30) are methanol, ethanol, isopropanol, and other lower alcohols; chloroform, dichloromethane, carbon tetrachloride, and other halogenated hydrocarbons; acetone; dimethylformamide; acetonitrile; and mixtures of the same. Inorganic acids such as hydrochloric acid, sulfuric acid, and hydrobromic acid may be added to the reaction. In the reaction, compound (30) is normally employed in a quantity of at

least 1 mole, preferably a quantity falling within a range of from 1 mole to about 50 moles, per mole of compound (29). The reaction is normally conducted at about 0 to 150°C, preferably about 0 to 100°C, and generally for a period of from about 10 minutes to 15 hours.

[Reaction Equation 14]



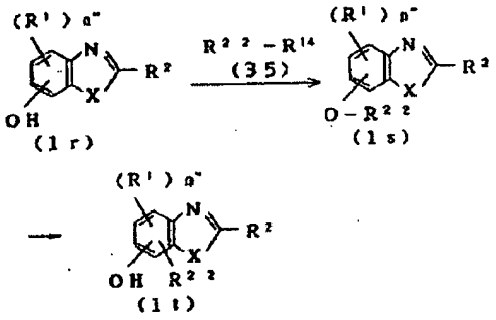
(In the equation, R^1, R^2, R^{14}, R^{19}, A, X, and n' are defined as above. R^{21} denotes a hydrogen atom or a lower alkyl group.)

The reaction between compounds (1f) and (31) is conducted under the same conditions as the reaction between compounds (1f) and (15) in above-described Reaction Equation 8.

The reaction between compounds (32) and (28) is conducted under the same conditions as the reaction between compounds (23) and (28) in above-described Reaction Equation 13.

The reaction between compounds (33) and (34) is conducted under the same conditions as the reaction between compounds (29) and (30) in above-described Reaction Equation 13.

[Reaction Equation 15]



(In the equation, R^1, R^2, X, and R^{14} are defined as above. n" denotes 0 or 1. R^{22} denotes a lower alkyl group or a phenyl lower alkyl group substituted on the phenyl ring with 1 to 3 substituents selected from the group consisting of lower alkyl groups and hydroxyl groups.)

The reaction between compounds (1r) and (35) is conducted under the same conditions as the reaction between compounds (1f) and (15) in above-described Reaction Equation 8.

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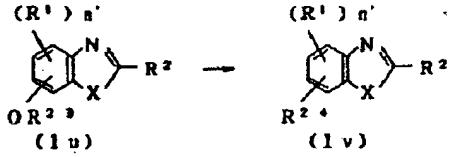
The reaction converting compound (1s) to compound (1t), normally referred to as a Claisen rearrangement, is conducted by heating the starting compounds in a suitable solvent. Examples of the solvent employed are dimethylformamide, diphenylether, dimethylaniline, tetrahydronaphthalene, and other solvents with high boiling points. The reaction is normally conducted at 100 to 250°C, preferably 150 to 250°C, for about 1 to 30 hours.

Compound (1t) can sometimes be directly obtained under the same conditions as the reaction of compounds (1r) and (35), depending on the type of group $-O-R^{22}$ of compound (1s) in the above-described reaction.

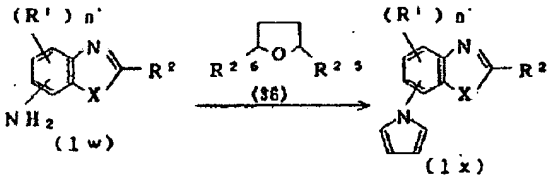
[Reaction Equation 16]



(In the equation, R^1, R^2, X, and n' are defined as above. R^{23} denotes an aminothiocarbonyl group optionally substituted with a lower alkyl group. R^{24} denotes an aminocarbonylthio group optionally substituted with a lower alkyl group.)

The reaction converting compound (1u) to compound (1v) is conducted in a suitable solvent by heating the starting compounds. Examples of the solvent employed are dimethylformamide, diphenylether, dimethylaniline, tetrahydronaphthalene, and other solvents with high boiling points. The reaction is normally conducted at 100 to 350°C, preferably about 150 to 300°C, for about 1 to 30 hours.

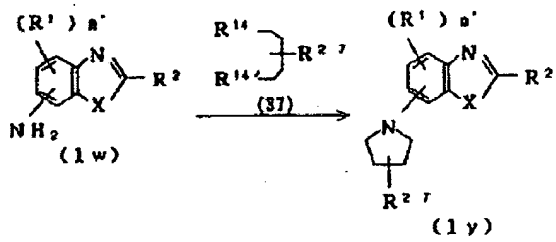
[Reaction Equation 17]



(In the equation, R^1, R^2, X, and n' are defined as above. Each of R^{25} and R^{26} denotes a lower alkoxy group.)

The reaction between compounds (1w) and (36) is conducted in a suitable solvent in the presence of an acid. Examples of the solvent employed here are water; methanol, ethanol, isopropanol, and other lower alcohols; acetone, methyl ethyl ketone, and other ketones; dioxane, tetrahydrofuran, ethyleneglycol dimethylether, and other ethers; acetic acid, formic acid, and other fatty acids; and mixtures of these solvents. Examples of the acid employed are: hydrochloric acid, sulfuric acid, hydrobromic acid, and other inorganic acids; formic acid, acetic acid, aromatic sulfonic acid, and other organic acids. The reaction is normally conducted at from about room temperature to 200°C, preferably at from about room temperature to 150°C, and generally for about 0.5 to 5 hours. Compound (36) is employed in a quantity of at least 1 mole, preferably from 1 mole to 2 moles, per mole of compound (1w).

[Reaction Equation 18]



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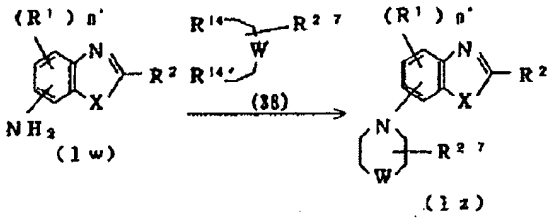
(In the equation, R^1, R^2, R^{14}, $R^{14'}$, X, and n' are defined as above. R^{27} denotes a hydrogen atom, an amino group optionally having a lower alkyl group, a lower alkyl group optionally substituted with a hydroxyl group, or an amino carbonyl group optionally substituted with a lower alkyl group.)

The reaction between compounds (1w) and (37) is conducted under the same conditions as the reaction between compounds (1f) and (15) of above-described Reaction Equation 8.

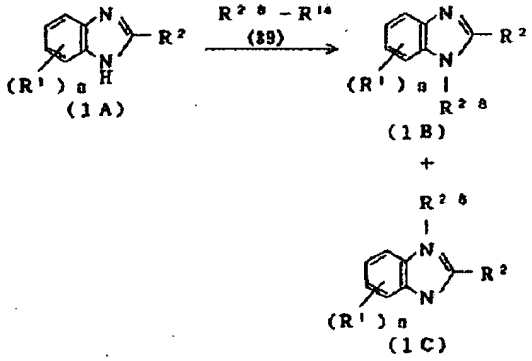
[Reaction Equation 19]



(In the equation, R^1, R^2, R^{14}, $R^{14'}$, R^{27}, X, and n' are defined as above, and w denotes the group $-CH_2-$ or a nitrogen atom.)

The reaction between compounds (1w) and (38) is conducted under the same conditions as the reaction between compounds (1f) and (15) of above-described Reaction Equation 8.

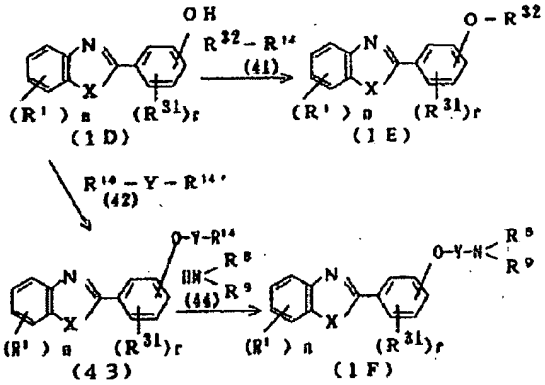
[Reaction Equation 20]



(In the equation, R^1, R^2, R^{14}, and n are defined as above. R^{28} denotes a lower alkyl group, a lower alkenyl group, or a phenyl lower alkyl group.)

The reaction between the compounds of general formulas (1A) and (39) can be conducted in a suitable solvent in the presence of a basic compound, for example. Examples of this basic compound are sodium hydride, potassium, sodium, sodium amide, and potassium amide. Examples of the solvent are dioxane, diethyleneglycol dimethylether, and other ethers; toluene, xylene, and other aromatic hydrocarbons; dimethylformamide; dimethylsulfoxide; and hexamethylphosphoric acid triamide. The proportions of compounds (1A) ad (39) are not specifically limited and may be suitably selected over a broad range. However, the latter is normally employed in a quantity of at least 1 mole, preferably from about 1 mole to 2 moles, per mole of the former. The reaction is normally conducted at from about 0 to 100°C, preferably about 0 to 70°C, and generally for about 0.5 to 1.2 hours.

[Reaction Equation 21]



(In the equation, R^1, R^8, R^9, R^{14}, Y, X, and n are defined as above. R^{22} denotes a lower alkyl group optionally having a halogen atom or the group $-Y-N<^{R^8}_{R^9}$ (wherein Y, R^8, and R^9 are defined as above). r denotes 0, 1, or 2. R^{31} denotes a lower alkoxy group optionally comprising a halogen atom, a lower alkyl group, a hydroxyl group, a hydrogen atom, or the group $-O-Y-N<^{R^8}_{R^9}$ (wherein Y, R^8, and R^9 are defined as above)).

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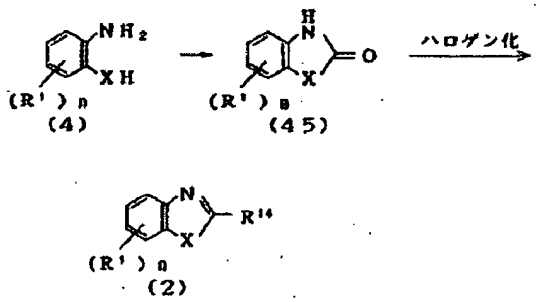
The reaction between compounds (1D) and (41) and the reaction between compounds (1D) and (42) are conducted under the same conditions as the reaction between compounds (1f) and (15) of above-described Reaction Equation 8.

The reaction between compounds (43) and (44) is conducted under the same conditions as the reaction between compounds (17) and (18) in above-described Reaction Equation 9.

The starting material (2) in above-described Reaction Equation 1 can be produced by the following method, for example.

[Reaction Equation 22]



[(upper right arrow) halogenation]

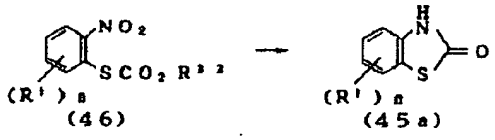
(In the equation, R^1, X, R^{14}, and n are defined as above.)

The reaction converting compound (4) to compound (45) is conducted by reacting the two compounds in a suitable solvent in the presence of a carbonylating agent. Examples of the solvent employed here are chlorobenzene, benzene, toluene, xylene, and other aromatic hydrocarbons, as well as diethylether, tetrahydrofuran, dioxane, and other ethers. Examples of the carbonylating agent are urea and N,N'-carbonyldiimidazole. The reaction is normally conducted at from room temperature to 200°C, preferably from about room temperature to 150°C, for a period of from about 1 to 10 hours. The carbonylating agent is employed in a quantity of at least 1 mole, preferably 1 to 2 moles, per mole of compound (4).

The halogenation reaction of compound (45) is conducted under the same conditions as the halogenation reaction of compound (25) of Reaction Equation 12.

Compound (45) can be prepared by the method of the reaction equation given below.

[Reaction Equation 23]



(In the equation, R^1 and n are defined as above. R^{33} denotes a lower alkyl group.)

The reaction converting compound (46) to compound (45a) is conducted by conducting reduction under the same conditions as in the reaction converting compound (12) to compound (1d) of above-described Reaction Equation 6, and then reacting the compounds in a solvent such as water or an alcohol such as methanol, ethanol, or isopropanol in the presence of an inorganic base such as sodium hydroxide, potassium hydroxide, sodium carbonate, or potassium carbonate, or an alkali metal alcoholate such as sodium methylate or sodium ethylate, usually at 0 to 100°C, preferably at about 0 to 70°C, for from 10 minutes to 5 hours. The reaction is advantageously promoted by adding hydrogen peroxide to the reaction system.

Compound (13), the starting material of Reaction Equation 7, can be produced by the method of the reaction equation given below, for example.

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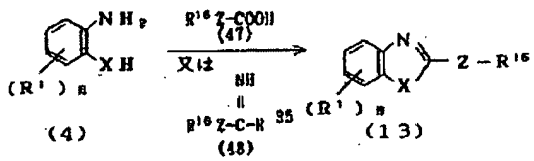
[Reaction Equation 24]



(In the equation, R^1, n, X, R^{16}, and Z are defined as above. R^{35} denotes a lower alkoxy group.)

The reaction between compounds (4) and (47) is conducted under the same conditions as the reaction between compounds (4) and (5) of above-described Reaction Equation 2.

The reaction between compounds (4) and (48) is conducted in a suitable solvent. Examples of the solvent employed here are: dichloromethane, chloroform, carbon tetrachloride, and other halogenated hydrocarbons; benzene, toluene, xylene, and other aromatic hydrocarbons; ethanol, methanol, isopropanol, and other alcohols; diethylether, tetrahydrofuran, dioxane, and other ethers; and dimethylsulfoxide, dimethylformamide, hexamethylphosphoric acid triamide, and other polar solvents. The reaction is normally conducted at 0 to 100°C, preferably from room temperature to close to 70°C, for about 10 to 80 hours.

Compound (48) may be employed in a quantity of at least 1 mole, preferably 1 to 3 moles, per mole of compound (4).

In the compound of general formula (1), when at least one of R^1 denotes a nitro group, conversion to a compound in which at least one of R^1 denotes an amino group is possible by reducing the nitro group.

The reduction reaction is conducted under the same conditions as the reaction converting compound (12) to compound (1d) in Reaction Equation 6. Additionally, a reduction method employing a catalytic reduction catalyst in a suitable solvent in the manner indicated below may be used.

Examples of the solvent employed are: water; acetic acid; methanol, ethanol, isopropanol, and other alcohols; hexane, cyclohexane, and other hydrocarbons; dioxane, tetrahydrofuran, diethylether, diethyleneglycol dimethylether, and other ethers; ethyl acetate, methyl acetate, and other esters; and N,N-dimethylformamide and other aprotic polar solvents. Examples of catalytic reduction catalysts are palladium, palladium-black, palladium-carbon, platinum, platinum oxide, copper chromite, and Raney nickel. The catalyst is generally employed in a quantity of about 0.02 to 1 time the quantity of starting material. The reaction temperature is normally about -20 to 150°C, preferably about 0 to 100°C. Normally, it suffices to maintain a hydrogen pressure of from 1 to 10 atmospheres. The reaction is generally conducted for about 0.5 to 10 hours.

For compounds in which at least one of R^1 in general formula (1) denotes a lower alkoxy group, or in which R^2 denotes a phenyl group having at least one substituent on the phenyl ring in the form of a lower alkoxy group, it is possible to derive a compound (1) in which at least one of R^1 denotes a hydroxyl group or in which R^2 denotes a phenyl group having at least one substituent on the phenyl ring in the form of a hydroxyl group by heat treatment at 30 to 150°C, preferably 50 to 120°C, in a mixture of an acid such as hydrobromic acid or hydrochloric acid and a solvent such as water, methanol, ethanol, or isopropyl alcohol. It is also possible to obtain a compound (1) in which at least one of R^1 denotes a hydroxyl group or in which R^2 denotes a phenyl group having at least one substituent on the phenyl ring in the form of a hydroxyl group by hydrolysis. The hydrolysis is conducted in a suitable solvent in the presence of an acid. Examples of the solvent are: water; methanol, ethanol, isopropyl alcohol, and other lower alcohols; dioxane, tetrahydrofuran, and other ethers; dichloromethane, chloroform, carbon tetrachloride, and other halogenated hydrocarbons; acetonitrile and other polar solvents; and mixtures of the same.

Examples of the acid are hydrochloric acid, sulfuric acid, hydrobromic acid, and other inorganic acids; boron trifluoride, aluminum chloride, boron tribromide, and other Lewis acids; sodium iodide, potassium iodide, and other iodides; and mixtures of these Lewis acids and iodides. The reaction is normally conducted at from room temperature to 150°C, preferably from room temperature to 100°C, generally for about 0.5 to 20 hours. The reaction may also be conducted in a solvent such as hexamethylphosphoric acid triamide or dimethylformamide in the presence of an alkylthiolithium salt such as n-butanethiolithium or t-butanethiolithium, or an alkylthioalkali metal salt such as ethanethiosodium.

In general formula (1), when R^2 denotes a five or six-membered saturated hetero ring comprising the group $-N<^{R^{12a}}_{R^{13a}}$ (wherein R^{12a} denotes a lower alkanoyl group and R^{13a} denotes a hydrogen atom, lower alkyl group, or lower alkanoyl group), in the same manner as when converting compound (11c) to compound (11) in above-described general formula 10, conversion to a compound in which the R^{12a} moiety of the group $-N<^{R^{12a}}_{R^{13a}}$ denotes a lower alkyl group is possible.

When R^2 in general formula (1) denotes a five or six-membered saturated hetero ring comprising the group $-N<^{R^{12a}}_{R^{13a}}$ (R^{12a} and R^{13a} being defined as above), or R^1 denotes $+O-A\rightarrow_m N<^{R^{4a}}_{R^{5b}}$ (wherein A, m, R^{4a}, and R^{5a} are defined as above), conversion to a compound in which the R^{12a} moiety in the group $-N<^{R^{12a}}_{R^{13a}}$ and the R^{5b} moiety in the group $+O-A\rightarrow_m N<^{R^{4a}}_{R^{5b}}$ denotes a hydrogen atom is possible by hydrolysis.

Any of the usual hydrolysis reaction conditions may be employed in the hydrolysis reaction. Specifically, hydrolysis is conducted in a solvent such as water; methanol, ethanol, isopropyl alcohol, or some other alcohol; acetone, methyl ethyl ketone, or some other ketone; dioxane, ethyleneglycol dimethylether, or some other ether; acetic acid; or a mixture of these solvents, in the presence of a basic compound such as sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, or barium hydroxide; an inorganic acid such as sulfuric acid, hydrochloric acid, or nitric acid; or an inorganic acid such as acetic acid or an aromatic sulfonic acid. The reaction is normally conducted at from room temperature to 200°C, preferably from about room temperature to 150°C, generally for about 0.5 to 20 hours.

When R^2 in general formula (1) denotes a five or six-membered saturated hetero ring comprising the group $-NH-R^{13a}$ (wherein R^{13a} is defined as above), the reaction can be conducted under the same conditions as in the reaction converting compound (1i) to compound (1j) in above-described Reaction Equation 10 to obtain a compound in which R^2 denotes a five or six-membered saturated hetero ring comprising the group $-N<^{R^{13a}}_{R^{12b}}$ (wherein R^{12b} denotes a lower alkyl group).

When R^2 in general formula (1) denotes the group $-N<^{R^{10}}_{R^{11}}$, R^{10} and R^{11} denote a hetero ring, and a phenyl lower alkoxycarbonyl group is present on the nitrogen atom, hydrolysis can be conducted under the same conditions as the hydrolysis reaction of the compound in which R^{12a} denotes a lower alkanoyl group to obtain a compound in which a hydrogen atom is present on the nitrogen atom.

When R^2 in general formula (1) denotes a phenyl group in which at least one lower alkyl group is present on the phenyl ring, the compound can normally be heated to from room temperature to 150°C, preferably from about 50 to 120°C for about 1 to 7 hours in an acid such as methanesulfonic acid or acetic acid to obtain a compound in which at least one of the lower alkyl groups on the phenyl ring is dealkylated.

When R^2 in general formula (1) denotes a pyrrolyl group, a reaction can be conducted under the same conditions as for the reaction of compounds (1A) and (39) of Reaction Equation 20 to obtain a compound in which one position on the pyrrolyl group is converted to a lower alkyl.

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When at least one among R^6 and R^7 denotes a hydrogen atom in general formula (1), the reaction can be conducted under the same conditions as the reaction of compounds (1i) and (19) in above-described Reaction Equation 10 to obtain a compound in which at least one among R^6 and R^7 denotes a lower alkyl group.

When at least one among R^8 and R^9 denotes a hydrogen atom in general formula (1), the reaction can be conducted under the same conditions as the reaction of compounds (1i) and (19) in above-described Reaction Equation 10 to obtain a compound in which at least one among R^8 and R^9 denotes a lower alkyl group or a cycloalkyl group.

When at least one among R^{10} and R^{11} or at least one among R^{12} and R^{13} denotes a hydrogen atom in general formula (1), the reaction can be conducted under the same conditions as the reaction of compounds (1i) and (19) in above-described Reaction Equation 10 to obtain a compound in which at least one among R^{10} and R^{11} or at least one among R^{12} and R^{13} denotes a lower alkyl group.

When at least one among R^{12} and R^{13} denotes a hydrogen atom in general formula (1), the reaction can be conducted under the same conditions as the reaction of compounds (1i) and (20) in above-described Reaction Equation 10 to obtain a compound in which at least one among R^{12} and R^{13} denotes a lower alkanoyl group.

The various target compounds thus obtained can be readily isolated and purified by the usual separation means. Examples of these separation means are: solvent extraction methods, dilution methods, recrystallization methods, column chromatography, and preparative thin-film chromatography.

The benzazole derivative of general formula (1) above may be in the form of a pharmaceutically acceptable acid or salt. Examples of such acids are: inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, and phosphoric acid, and organic acids such as oxalic acid, succinic acid, malic acid, fumaric acid, acetic acid, maleic acid, citric acid, and lactic acid.

Among the benzazole derivatives of general formula (1) above, compounds having acidic groups may be in the form of pharmaceutically acceptable bases and salts. Examples of such bases are alkali metal and alkaline earth metal hydroxides such as sodium hydroxide, potassium hydroxide, and calcium hydroxide.

The compound of the present invention covers optical isomers and stereoisomers.

The compound of the present invention is employed in the form of common pharmaceutical formulations. These formulations may be prepared with commonly employed fillers, bulking agents, binders, moisturizers, anticaking agents, surfactants, diluents such as gloss imparting agents, and excipients. Various forms of medical formulations may be selected based on the treatment objective. Examples of typical formulations are tablets, pellets, powders, liquids, suspensions, emulsions, granules, capsules, suppositories, and injections (liquids, suspensions, and the like). When preparing a tablet, carriers that are conventionally known in the field may be widely employed. Examples are lactose, cane sugar, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose, silicic acid, and other excipients; water, ethanol, propanol, simple syrup, glucose solutions, starch solutions, gelatin solutions, carboxymethyl cellulose, shellac, methyl cellulose, potassium phosphate, polyvinyl pyrrolidone, and other binders; dry starch, sodium alginate, agar powder, laminaran powder, sodium bicarbonate, calcium carbonate, polyoxyethylene sorbitan fatty esters, sodium lauryl sulfate, stearic acid monoglyceride, starch, lactose, and other anticaking agents; cane sugar, stearin, cocoa butter, hydrogenated oils, and other antidisintegrating agents; quaternary ammonium salts, sodium lauryl sulfate, and other absorption promoters; glycerin, starch, and other moisturizers; colloidal silicic acid and other adsorbants; and pure talc, stearate, boric acid powder, polyethylene glycol, and other lubricants.

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Tablets may be treated with the usual coatings as needed; examples are sugar-coated tablets, gelatin-coated tablets, enteric coated tablets, film-coated tablets, double tablets, and multilayered tablets. When forming pellets, any of the carriers conventionally known in the field may be widely employed; examples are glucose, lactose, starch, cocoa oil, hardened vegetable oil, kaolin, talc, and other excipients; gum arabic powder, traganth powder, gelatin, ethanol, and other binders; and laminaran, agar, and other anticaking agents. When forming suppositories, any of the carriers conventionally known in the field may be widely employed; examples are polyethylene glycol, cocoa oil, higher alcohols, esters of higher alcohols, gelatin, and semisynthetic glyceride. When preparing an injection, the solution, emulsion, or suspension is sterilized and desirably rendered isotonic with blood. When forming such a solution, emulsion, or suspension, all diluting agents normally employed in the field may be employed; examples are water, lactic acid aqueous solutions, ethyl alcohol, propylene glycol, ethoxy-treated isostearyl alcohol, polyoxy-treated isostearyl alcohol, and polyoxyethylene sorbitan fatty esters. When preparing an isotonic solution, an adequate quantity of edible salt, glucose, or glycerin may be incorporated into the pharmaceutical formulation. The usual dissolution adjuvants, buffering agents, analgesics, and the like may also be added. Further, as needed, coloring agents, preservatives, fragrance materials, flavoring agents, sweeteners, and the like, as well as other pharmaceutical products, may be incorporated into pharmaceutical formulations. When forming pastes, creams, and gels, it is possible to employ

diluting agents such as white vaseline, paraffin, glycerin, cellulose derivatives, polyethylene glycol, silicon, bentonite, and the like.

The quantity of the compound of general formula (1), or a salt thereof, that is to be incorporated into the pharmaceutical formulation of the present invention is not specifically limited and may be suitably selected over a wide range. However, the use of 1 to 70 weight percent of the total composition normally suffices.

The method of administering the pharmaceutical formulation of the present invention is not specifically limited. The method of administration is based on the various types of formulations; the age, sex, and other conditions of the patient; the severity of the disease; and the like. For example, tablets, pellets, solutions, suspensions, emulsions, granules and capsules may be administered orally. Injections, may be administered intravenously, either independently or in combination with the usual auxiliary solutions, such as glucose, amino acids, and the like. Injections may also be injected independently into muscle, into the skin, subcutaneously, or into the abdominal cavity, as necessary. Suppositories may be administered into the rectum.

The dosage of the pharmaceutical composition of the present invention that is administered is suitably selected based on the method employed; the age, sex, and other conditions of the patient; the severity of the disease; and the like. The dosage of the compound of general formula (1), which is normally an active ingredient, may be about 0.06 to 100 mg per kg of body weight daily. The formulation may also be administered in 2 to 4 installments per day.

Embodiments

Formulation examples, reference examples, embodiments, and pharmacological tests are described below.

Formulation Example 1

Preparation of tablets

Formulation	Quantity (g)
6-Trifluoromethyl-2-(2-thienyl)benzimidazole	5
Lactose (Japanese Pharmacopoeia product)	50
Cornstarch (Japanese Pharmacopoeia product)	25
Crystalline cellulose (Japanese Pharmacopoeia product)	25
Methyl cellulose (Japanese Pharmacopoeia product)	1.5
Magnesium stearate (Japanese Pharmacopoeia product)	1

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The above-listed compound of the present invention, lactose, cornstarch, and crystalline cellulose were thoroughly mixed, granulated with a 5 percent aqueous solution of methyl cellulose, passed through a 200-mesh sieve, and carefully dried. This product was then tableted by the usual method to prepare 1,000 tablets.

Manufacturing Example 2

Preparation of capsules

Formulation	Quantity (g)
6-Hydroxy-(2-methoxyphenyl)benzthiazole	10
Lactose (Japanese Pharmacopoeia product)	80
Starch (Japanese Pharmacopoeia product)	30
Talc (Japanese Pharmacopoeia product)	5
Magnesium stearate (Japanese Pharmacopoeia product)	1

The above-listed components were finely powdered, thoroughly stirred to obtain a fine mixture, and packed into gelatin capsules of desired size for oral administration to prepare 1,000 capsules.

Manufacturing Example 3

Preparation of an injection

Formulation	Quantity (g)
6-(Dimethylaminocarbonylthio)-2-(1-methyl-2-pyrrolyl)benzthiazole	1
Polyethylene glycol (molecular weight: 4,000) (Japanese Pharmacopoeia product)	0.3
Sodium chloride (Japanese Pharmacopoeia product)	0.9
Polyoxyethylene sorbitan monooleate (Japanese Pharmacopoeia product)	0.4
Sodium metabisulfite	0.1
Methylparaben (Japanese Pharmacopoeia product)	0.18
Propylparaben (Japanese Pharmacopoeia product)	0.02

Injection-use distilled water 100 (mL)

While stirring, the above-listed parabens, sodium bisulfite, and sodium chloride were dissolved in roughly half of the above distilled water at 80°C. This solution was then cooled to about 40°C. The compound of the present invention, polyethylene glycol, and polyoxyethylene sorbitan monooleate were dissolved in the solution, the [remainder of the] injection-use distilled water was added to this solution to obtain the final quantity, and suitable filter paper was employed for sterilization filtration to prepare an injection.

Reference Example 1

A 30 g quantity of 2-mercapto-4-chloroaniline and 20 g of urea were added to 400 mL of chlorobenzene and the mixture was stirred with heating for 6 hours at 130°C under a nitrogen atmosphere. The solvent was removed by decantation. The residual crystals were collected by filtration and washed with diethylether, yielding 17.8 g of 6-chlorobenzthiazole-2-one.

Melting point: 192-195°C

Reference Example 2

A 5 g quantity of 6-chlorobenzthiazole-2-one was added to 30 mL of phosphorus oxychloride and hot refluxed for 10 hours. The mixture was poured into ice water and extracted with chloroform. The chloroform layer was washed with water and dried (magnesium sulfate). The solvent was removed under reduced pressure. The residue was refined by silica gel chromatography (methylene chloride) and recrystallized from n-hexane, yielding 2.7 g of 2,6-dichlorobenzthiazole in the form of colorless acicular crystals.

Melting point: 93-94°C

The following compounds were obtained in the same manner as in Reference Example 2.

* 2,7-Dichlorobenzthiazole

Melting point: 49-50°C (recrystallized from n-hexane), colorless, acicular

* 2,6-Dichloro-4-methylbenzthiazole

NMR ($CDCl_3$) δ:

2.67 (3H, s)
7.28 (1H, m)
7.58 (1H, m)

* 2,5-Dichlorobenzthiazole

Melting point: 65-66°C (recrystallized from n-hexane), colorless, tabular

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* 2-Chloro-6-(1-piperidinyl)benzthiazole

Melting point: 66-67°C (recrystallized from ethyl acetate-n-hexane), pale yellow, prismatic

* 2-Chloro-6-ethoxy-4-nitrobenzthiazole

Melting point: 174.5-175.5°C (recrystallized from chloroform-n-hexane), pale yellow, acicular

* 2-Chloro-6-methoxy-5-nitrobenzthiazole

Light brown, prismatic (recrystallized from methylene chloride-n-hexane)

NMR ($CDCl_3$) δ:

1.52 (3 H, t, J = 7 Hz)
4.22 (2 H, q, J = 7 Hz)
7.40 (1 H, s)
8.33 (1 H, s)

Reference Example 3

A 5 g quantity of 2-ethoxycarbonylmethio-5-chloronitrobenzene and 5.3 g of reduced iron were added to 40 mL of methanol. While hot refluxing this mixture, 10 mL of concentrated hydrochloric acid was added dropwise over 30 minutes. Thereafter, 10 mL of concentrated hydrochloric acid was added dropwise each hour and hot refluxing was conducted for three hours. The reaction solution was subjected to thermal-time cerite filtration and the residue was washed with acetone. The mother solution and acetone-washed solution were concentrated, water was added, and the precipitating crystals were collected by filtration. The precipitating crystals were added to 50 mL of water containing 0.6 g of sodium hydroxide and the mixture was stirred for 0.5 hour. To this were added three drops of 28 percent hydrogen peroxide solution and 0.5 g of activated carbon and the mixture was stirred for another 0.5 hour. The insoluble matter was filtered out and the mother solution was neutralized with 10 percent chloride. The precipitating crystals were collected by filtration, washed with water, and dried, yielding 2.4 g of 5-chlorobenzthiazole-2-one in the form of a white powder.

NMR: δppm ($DMSO-d_6$):

7.13 (1 H, d, J = 2, 1 Hz)
7.20 (1 H, d-d, J = 2.1, 8.3 Hz)
7.63 (1 H, d, J = 8.4 Hz)
11.5 (1 H, br-s)

Reference Example 4

A 25 g quantity of 2-chloro-4-nitroaniline and 22 g of triethylamine were added to 300 mL of chloroform, the mixture was cooled on ice, 30 mL of a methylene chloride solution of 29.6 g of o-methoxybenzoylchloride was added dropwise, and the mixture was stirred overnight at room temperature. The chloroform was distilled off, water was added to the residue to induce crystallization, ethanol was added,

and the product was recovered by filtration. This product was washed with ethanol and dried, yielding 28 g of 3-chloro-4-(o-methoxybenzoylamino)nitrobenzene.

Reference Example 5

A 28 g quantity of 3-chloro-4-(o-methoxybenzoylamino)nitrobenzene and 22 g of phosphorus pentasulfide were added to 300 mL of toluene and the mixture was stirred overnight with heating at 100°C. The mixture was poured into ice water and extracted with chloroform. The chloroform layer was washed with water and dried (sodium sulfate). The solvent was distilled off under reduced pressure. The residue was recrystallized from ethanol, yielding 19.7 g of 3-chloro-4-(o-methoxythiobenzoylamino)nitrobenzene in the form of orange acicular crystals (melting point: 132-136°C).

Reference Example 6

A 2 g quantity of 4-hydroxy-3-t-butylbenzoate was added to 20 mL of thionyl chloride, one drop of dimethylformamide was added, and the mixture was stirred for 2 hours at room temperature. Following concentration under reduced pressure, dry chloroform was added, and three cycles of azeotropic distillation were conducted. The product was dissolved in 5 mL of dry chloroform and this solution was added dropwise at room temperature to a mixture of 1.89 g of 4-cyano-2-bromoaniline, 0.12 g of 4-dimethylaminopyridine, and 10 mL of pyridine. After stirring overnight at room temperature, the pyridine was distilled off under reduced pressure. Ethanol was added and the precipitating crystals were recovered by filtration. The crystals were washed with a 1:2 mixture of ethanol:diethylether and then recrystallized from ethanol, yielding 2.93 g of 3-bromo-4-(4-methoxy-3-t-butylbenzoylamino)benzonitrile in the form of a white powder.

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Melting point: 181-182°C

Reference Example 7

A 2.7 g quantity of 3-bromo-4-(4-methoxy-3-t-butylbenozylamino)benzonitrile and 2.82 g of 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetan-2,4-disulfide were added to 100 mL of xylene and the mixture was stirred with heating for 2 hours at 110°C. The xylene was distilled off under reduced pressure, saturated sodium bicarbonate aqueous solution was added, and the mixture was extracted with methylene chloride. The methylene chloride layer was washed with water and dried (sodium sulfate), and the solvent was distilled off under reduced pressure. The mixture was recrystallized from ethanol-n-hexane, yielding 1.5 g of 3-bromo-4-(4-methoxy-3-t-butylbenzoylamino)benzonitrile in the form of yellow acicular crystals.

Melting point 188-189°C

In the same manner as in above-described Reference Examples 5 and 7, 3-chloro-4-(4-methoxy-3-t-butylthiobenzoylamino)nitrobenzene was obtained.

Melting point: 185°C (sublimation)

Colorless flakes (recrystallized from xylene)

Reference Example 8

A 1.2 g quantity of 3,4-diaminobenztrifluoride and 1.4 g of N,N'-carbonyldimidazole were added to 20 mL of anhydrous tetrahydrofuran and the mixture was hot refluxed for 9 hours under a nitrogen flow. The mixture was poured into water and the precipitating crystals were collected by filtration, washed with water, and dried, yielding 1.3 g of 5-trifluoromethyl-2-benzimidazolone in the form of a white powder.

Reference Example 9

A 1.3 g quantity of 5-trifluoromethyl-2-benzimidazolone was added to 20 mL of phosphorus oxychloride and the mixture was hot refluxed for 3 hours. Following concentration under reduced pressure, water was added to the residue and the mixture was extracted with chloroform. The chloroform layer was washed with water and dried (sodium sulfate). The solvent was distilled off under reduced pressure. n-Hexane was added to the residue to precipitate crystals. The crystals were collected by filtration and dried, yielding 0.9 g of 2-chloro-5-trifluoromethylbenzimidazole in the form of a white powder.

Reference Example 10

An 18.7 g quantity of methyl chloroacetoimido acid hydrochloride was added in small increments and with ice cooling to a methylene chloride solution (300 mL) of 14.3 g of 2-amino-4-chloroaniline. Following the addition, the mixture was stirred for two days at room temperature and a further 10 g of methyl chloroacetoimido acid hydrochloride was added. The mixture was stirred for 1 day. The methylene chloride layer was washed with saturated sodium bicarbonate aqueous solution and water, and then dried (sodium sulfate). Following concentration under reduced pressure, the residue was refined by silica gel chromatography (chloroform:ethyl acetate:n-hexane = 1:1:1) and recrystallized from chloroform-n-hexane, yielding 13 g of 2-chloromethyl-5-chlorobenzimidazole in the form of a light brown powder.

NMR: δppm ($CDCl_3$):

4.85 (2 H, s)
7.27 (1 H, d-d, J = 2, 8.5 Hz)
7.33 - 7.90 (2 H, m)
9.96 (1 H, br-s)

Reference Example 11

A 2.9 g quantity of 2-amino-4-chloroaniline and 2.5 g of chloroacetic acid were added to 50 mL of 4 N hydrochloric acid and the mixture was hot refluxed for 2 hours. The mixture was neutralized with ammonia water, water was added, and the mixture was extracted with chloroform. The chloroform layer was washed with water and dried (sodium sulfate). The solvent was distilled off under reduced pressure. The residue was refined by silica gel chromatography (methylene chloride:methanol = 30:1), yielding 0.6 g of 2-chloromethyl-5-chlorobenzimidazole in the form of pale yellow crystals.

NMR: δppm ($CDCl_3$):

4.85 (2 H, s)

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7.27 (1 H, d-d, J = 2, 8.5 Hz)
7.33 - 7.90 (2 H, m)
9.96 (1 H, br-s)

Reference Example 12

A 3.4 g quantity of 2-thenoylchloride was added dropwise to 40 mL of a pyridine solution of 4 g of 3-nitro-4-aminobenzotrifluoride and 0.12 g of 4-dimethylaminopyridine. The mixture was stirred for 3 hours at room temperature and poured into ice water. The precipitating crystals were collected by filtration. The crystals were dissolved in ethyl acetate; washed with 1 N hydrochloric acid, water, saturated sodium bicarbonate aqueous solution, and water; and dried (sodium sulfate). Following concentration under reduced pressure, recrystallization was conducted from ethyl acetate-n-hexane, yielding 1.6 g of 3-nitro-4-(2-thenoylamino)benzotrifluoride in the form of yellow acicular crystals.

Reference Example 13

A 1 g quantity of 4-nitro-o-phenylenediamine and 40 mg of 4-dimethylaminopyridine were dissolved in 10 mL of pyridine and 0.96 g of 2-thenoylchloride was added with ice cooling. After stirring at room temperature overnight, the pyridine was distilled off under reduced pressure, 5 percent hydrochloric acid was added, and the mixture was extracted with methylene chloride. The organic layer was washed with water, dried (magnesium sulfate), and concentrated under reduced pressure. The crystals that precipitated were collected by filtration and recrystallized from methylene chloride, yielding 1 g of 2-(2-thenoylamino)-5-nitroaniline in the form of yellow granular crystals.

Melting point: 205-205°C

Reference Example 14

A 2 g quantity of 2-(3,5-t-butyl-4-hydroxyphenyl)-6-(3-cyanopropoxy)benzthiazole was added to a mixed solution of 100 mL of chloroform and 10 mL of ethanol. With methanol and ice cooling, Hydrochloric acid gas was passed through. The mixture was left standing overnight at 5°C, poured into an ice water sodium chloride solution, and extracted with chloroform. The chloroform layer was washed with water and dried (sodium sulfate). The solvent was distilled off under reduced pressure, yielding 2.2 g of 2-(3,5-di-t-butyl-4-hydroxyphenyl)-6-(3-ethoxy-3-iminopropoxy)benzthiazole in the form of a pale green, oily substance.

NMR: δppm ($CDCl_3$):

1. 30 (3 H, t, J = J Hz)
2. 51 (18 H, s)
2.10 (2 H, m)
2.48 (2 H, t, J = 7 Hz)
4.06 (2 H, t, J = 7 Hz)
4.13 (2 H, q, J = 7 Hz)

5.54 (1 H, s)
7.03 (1 H, d-d, J = 9, 2.5 Hz)
7.31 (2 H, d, J = 2.5 Hz)
7.85 (2 H, s)
7.90 (2 H, d, J = 9 Hz)

Embodiment 1

A 1 g quantity of 2,6-dichlorobenzthiazole and 4.2 g of piperazine were added to 30 mL of α-picoline and the mixture was stirred with heating for 5 hours at 100°C. Following concentration under reduced pressure, water was added to the residue and the mixture was extracted with chloroform. The chloroform layer was washed with water and dried (sodium sulfate). The solvent was distilled off under reduced pressure. The residue was refined by silica gel chromatography (methylene chloride:methanol = 8:1). Hydrochloric acid was added and the mixture was concentrated and solidified. The mixture was recrystallized from wet ethanol, yielding 0.31 g of 2-piperazino-6-chlorobenzthiazole hydrochloride in the form of colorless tabular crystals.

NMR: δppm (DMSO-d_6):

3.2-3.4 (4 H, m)
3.8-4.0 (4 H, m)
7.35 (1 H, d-d, J = 2.1, 8.6 Hz)
7.51 (1 H, d, J = 8.6 Hz)
7.99 (1 H, d, J=2.2 Hz)

Embodiment 2

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A 0.6 g quantity of 2-chloro-6-trifluoromethylbenzimidazole was added to 5 mL of 3-chloroaniline and the mixture was stirred with heating for 2 hours at 140°C under a nitrogen atmosphere. Following concentration under reduced pressure, water was added to the residue and the mixture was extracted with methylene chloride. The methylene chloride layer was washed with water and dried (sodium sulfate). The solvent was distilled off under reduced pressure. The residue was refined by silica gel chromatography (methylene chloride:methanol = 20:1), converted to an oxalate in acetone, and recrystallized from wet ethanol, yielding 0.3 g of 2-(3-chlorophenylamino)-6-trifluoromethylbenzimidazole oxalate in the form of a white powder.

Melting point: 247-250°C (decomposition)

Embodiment 3

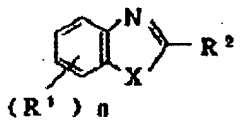
A 3 g quantity of 2,6-dichlorobenzthiazole, 5 g of 4-acetoamidopiperidine hydrochloride, and 2 mL of DBU were added to 50 mL of 2,6-lutidine and the mixture was stirred with heating for 8 hours at 100°C. Following concentration under reduced pressure, water was added to the residue and the mixture was extracted with chloroform. The chloroform layer was washed with water and dried (sodium sulfate). The solvent was distilled off under reduced pressure. The residue was refined by silica gel chromatography (methylene chloride:methanol = 20:1). The product was

recrystallized from chloroform, yielding 2.5 g of 2-(4-acetoamidopiperidino)-6-chlorobenzthiazole.

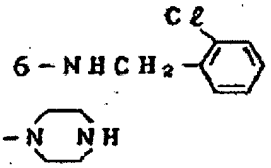
Melting point: 234-235°C

The compounds indicated in Table 1 below were obtained using suitable starting materials in the same manner as in Embodiments 1, 2, and 3.

Table 1



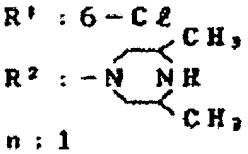
Embodiment 4
Structure



R^1:

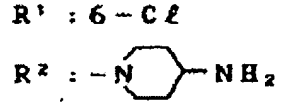
R^2:
n: 1
X: S
Form of crystals: light brown powder
Recrystallization solvent: ethanol - diethylether
Melting point: 215-218°C (decomposition)
Form: 3HCl

Embodiment 5
Structure



n : 1
X : S
Form of crystals: colorless needles
Recrystallization solvent: ethyl acetate - n-hexane
Melting point: 99-100°C
Form: free

Embodiment 6
Structure



n : 1 X : S
Form of crystals: brown flakes
Recrystallization solvent: ethanol - water
Melting point: 300°C or higher
NMR analysis results: 1)

Form: HCl

Embodiment 7
Structure
R¹ : 5-Cℓ

n : 1 X : S
Form of crystals: colorless needles
Recrystallization solvent: ethanol - water
Melting point: 320°C or higher
NMR analysis results: 2)
Form: HCl

Embodiment 8
Structure
R¹ : 7-Cℓ

n : 1 X : S
Form of crystals: colorless needles
Recrystallization solvent: ethanol - water
Melting point: 320°C or higher
NMR analysis results: 3)
Form: HCl

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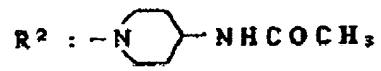
Embodiment 9
Structure
R¹ : 4, 6-diCℓ

n : 2
X : S
Form of crystals: colorless flakes
Recrystallization solvent: ethanol - water
Melting point: 300°C or higher
NMR analysis results: 4)
Form: 2HCl

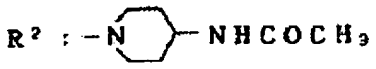
Embodiment 10
Structure
R¹ : 4, 6-diCℓ



n : 2
X : S
Form of crystals: colorless needles
Recrystallization solvent: chloroform - diethylether
Melting point: 252-253°C
Form: free

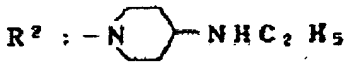
Embodiment 11
Structure

R^1 : 6-$OCH_2COOC_2H_5$

R^2 : 

n : 1
X : S
Form of crystals: colorless needles
Recrystallization solvent: dichloromethane - n-hexane
Melting point: 147-148.5°C
Form: free

Embodiment 12
Structure
R^1 : 6-Cℓ

R^2 : 

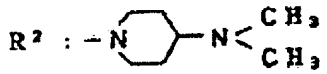
n : 1
X : S
Form of crystals: white powder
Recrystallization solvent: ethanol - water
Melting point: 300-302°C
Form: HCl

Embodiment 13
Structure
R^1 : 6-Cℓ

R^2 : 

n : 1
X : S
Form of crystals: white powder
Recrystallization solvent: dichloromethane - n-hexane
Melting point: 166-167°C
Form: free

Embodiment 14
Structure
R^1 : 6-Cℓ

R^2 : 

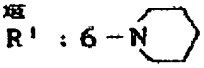
n : 1
X : S
Form of crystals: white powder
Recrystallization solvent: ethanol - water
Melting point: 285°C (decomposition)
Form: HCl

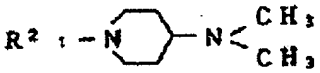
Embodiment 15
Structure

R^1 : 4-CH_3
6-Cl

R^2 : 

n : 2
X : S
Form of crystals: white powder
Recrystallization solvent: ethanol - ethyl acetate
Melting point: 262-266°C
Form: 2HCl

Embodiment 16
Structure
R^1 : 6- 

R^2 : 

n : 1
X : S
Form of crystals: white powder
Recrystallization solvent: isopropyl alcohol - water
Melting point: 292-293°C (decomposition)
Form: 2HCl

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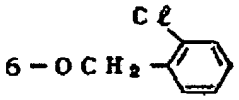
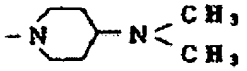
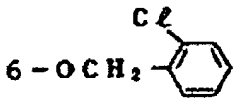
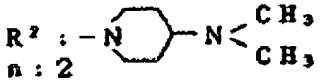
Embodiment 17
Structure
R^1: 

R^2: 

n: 1
X: S
Form of crystals: white powder
Recrystallization solvent: isopropyl alcohol - water
Melting point: 244-245°C
Form: HCl

Embodiment 18
Structure
R^1 : 4-$NHCOCH_3$

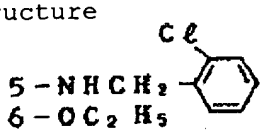


R^2 : 

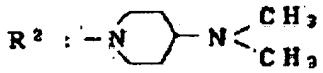
n : 2
X : S
Form of crystals: white powder
Recrystallization solvent: ethanol - hydrochloric acid
Melting point: 215-217°C (decomposition)

Form: 2HCl

Embodiment 19
Structure

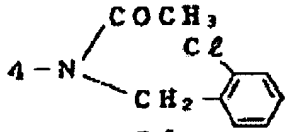


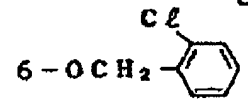
R^1:



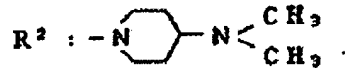
n : 2
X : S
Form of crystals: colorless needles
Recrystallization solvent: chloroform - n-hexane
Melting point: 158.5-161.5°C
Form: free

Embodiment 20
Structure



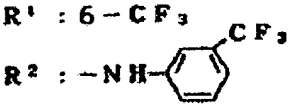


R^1:



n : 2
X : S
Form of crystals: white powder
Recrystallization solvent: chloroform - n-hexane
Melting point: 180-181°C
Form: free

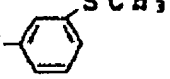
Embodiment 21
Structure



n : 1
X : NH
Form of crystals: pale yellow, undefined shape
NMR analysis results: 5)
Form: free

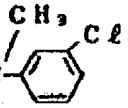
Embodiment 22
Structure

R^1 : 6-CF_3

R^2 : -NH- 

n : 1
X : NH
Form of crystals: pale peach-colored powder
Recrystallization solvent: ethanol - n-hexane
Melting point: 222-224°C (decomposition)
Form: $(COOH)_2$

Embodiment 23
Structure
R^1 : 6-CF_3

R^2 : -N- 

n : 1
X : NH
Form of crystals: colorless needles
Recrystallization solvent: dichloromethane - n-hexane
Melting point: 213-215.5°C
Form: free

Embodiment 24
Structure
R^1 : 6-NO_2

R^2 : -N N-CO_2CH_2- 

n : 1
X : S
Form of crystals: yellow powder
Recrystallization solvent: chloroform - diethylether
Melting point: 186-190°C
Form: free

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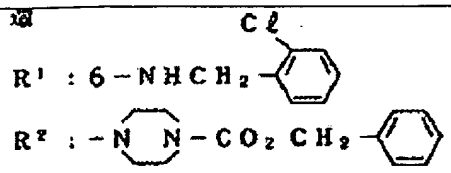
Embodiment 25
Structure
R^1 : 6-NH_2

R^2 : -N N-CO_2CH_2- 

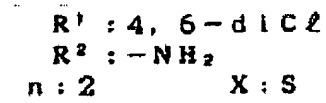
n : 1
X : S
Form of crystals: pale yellow flakes
Recrystallization solvent: ethanol
Melting point: 126-129°C
Form: free

Embodiment 26
Structure



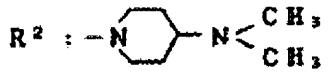
n : 1
X : S
Form of crystals: colorless needles
Recrystallization solvent: ethanol - n-hexane
Melting point: 111-114°C
Form: free

Embodiment 27
Structure



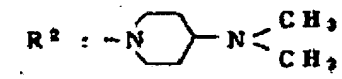
Form of crystals: white powder
NMR analysis results: 6)
Form: free

Embodiment 28
Structure



Form of crystals: white powder
Recrystallization solvent: ethanol - water
NMR analysis results: 7)
Form: free

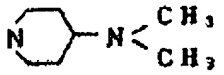
Embodiment 29
Structure



Form of crystals: pale yellow needles
Recrystallization solvent: ethyl acetate
Melting point: 149-151°C
Form: free

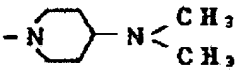
Embodiment 30
Structure

R^1 : 4-NH_2
6-OC_2H_5

R^2 : 

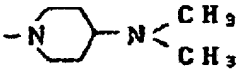
n : 2
X : S
Form of crystals: colorless needles
Recrystallization solvent: ethyl acetate - n-hexane
Melting point: 142-143°C
Form: free

Embodiment 31
Structure
R^1 : 4-NH_2
6-OH

R^2 : 

n : 2
X : S
Form of crystals: gray powder
Recrystallization solvent: dimethylformamide - diethylether
Melting point: 255-260°C
Form: free

Embodiment 32
Structure
R^1 : 4-$NHCOCH_3$
6-OH

R^2 : 

n : 2
X : S
Form of crystals: colorless needles
Recrystallization solvent: methanol - water
Melting point: 230-232°C
Form: free

/42

Embodiment 33

While suspending 5 g of 2-amino-5-ethoxythiophenol and 3.5 g of pyridine in 120 mL of toluene by stirring, 6 g of o-methoxybenzoylchloride was added dropwise. Following 8 hours of hot refluxing, the mixture was poured into water and extracted with chloroform. The chloroform layer was washed with water and dried (sodium sulfate). The solvent was distilled off under reduced pressure. Ethanol was added to the residue and the precipitating crystals were collected by filtration. The crystals obtained were dissolved in 60 mL of methane sulfonic acid, 6 g of phosphorus pentoxide was added, and the mixture was stirred with heating for 4 hours at 80°C. The mixture was poured into ice water and extracted with chloroform. The chloroform layer was washed with water and dried (sodium sulfate).

The solvent was distilled off under reduced pressure. The residue was refined by silica gel chromatography (methylene chloride:n-hexane = 1:1). The produce was recrystallized from n-hexane, yielding 1.6 g of 2-(2-chlorophenyl)-6-ethoxybenzthiazole in the form of pale yellow, acicular crystals.

Melting point: 75-75.5°C

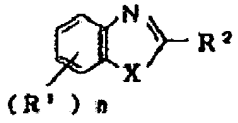
Embodiment 34

A 0.1 g quantity of 2-(2-thenoylamino)-5-nitroaniline was added to 3 mL of 6 N hydrochloric acid and the mixture was hot refluxed for 0.5 hours. Water was added and the mixture was allowed to cool. The precipitating crystals were collected by filtration and recrystallized from water, yielding 70 mg of 2-(2-thienyl)-6-nitrobenzimidazole hydrochloride in the form of colorless acicular crystals.

Melting point: 150-152°C

The various compounds indicated in Table 2 below were obtained using suitable starting materials in the same manner as in Embodiments 33 and 34. The NMR analysis results of these compounds are given in Table 3.

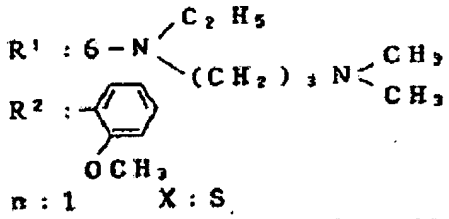
Table 2



Embodiment 35 Structure R^1 : 6-OH R^2 :  n : 1 X : S Form of crystals: Pale yellow prisms Recrystallization solvent: ethanol - water Melting point: 190-195°C Form: free
Embodiment 36 Structure R^1 : 6-O $(CH_2)_3$ $N<^{CH_3}_{CH_3}$ R^2 :  n : 1 X : S Form of crystals: white powder Recrystallization solvent: ethanol Melting point: 163-164°C

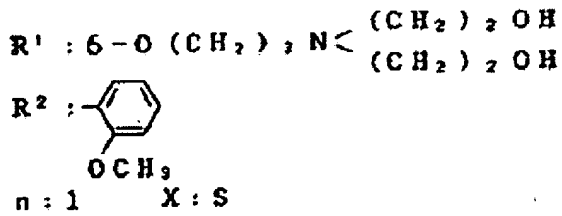
Form: $(COOH)_2$

Embodiment 37
Structure



n : 1 X : S
Form of crystals: pale yellow powder
Recrystallization solvent: ethanol
Melting point: 180.5-183°C (decomposition)
Form: $(COOH)_2$

Embodiment 38
Structure



n : 1 X : S
Form of crystals: colorless prisms
Recrystallization solvent: n-hexane - diethylether
Melting point: 83.0-85.5°C
Form: free

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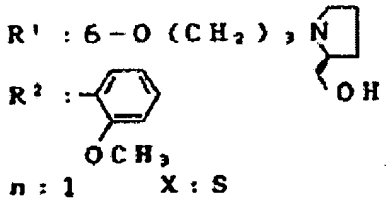
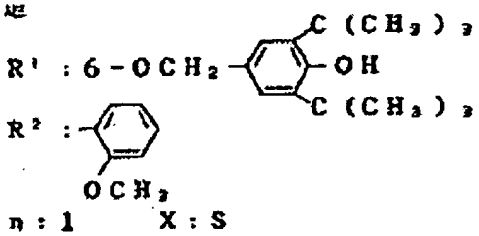
Embodiment 39
Structure



n : 1 X : S
Form of crystals: colorless grains
Recrystallization solvent: chloroform - n-hexane
Melting point: 49.0-51.0°C
Form: free

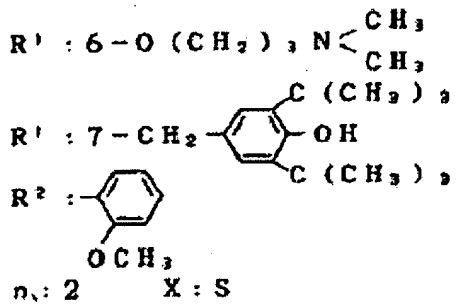
Embodiment 40
Structure



n : 1 X : S
Form of crystals: colorless needles
Recrystallization solvent: ethyl acetate - n-hexane
Melting point: 145-146°C

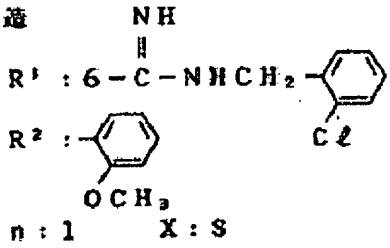
Form: free

Embodiment 41
Structure



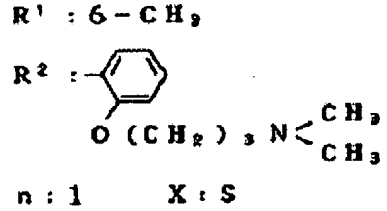
Form of crystals: colorless needles
Recrystallization solvent: ethyl acetate - n-hexane
Melting point: 134-135°C
Form: free

Embodiment 42
Structure



Form of crystals: white powder
Recrystallization solvent: chloroform
Melting point: 275-277°C (decomposition)
Form: free

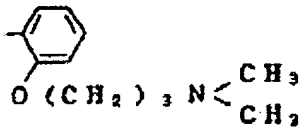
Embodiment 43
Structure



Form of crystals: white powder
Recrystallization solvent: ethanol - water
Melting point: 195-196°C (decomposition)
Form: $(COOH)_2$

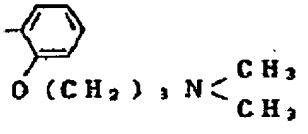
Embodiment 44
Structure

R^1 : 6-F

R^2 : 

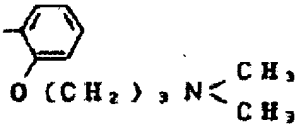
n : 1 X : S
Form of crystals: colorless prisms
Recrystallization solvent: ethanol - water
Melting point: 205-206°C (decomposition)
Form: $(COOH)_2$

Embodiment 45
Structure
R^1 : 6-Cℓ

R^2 : 

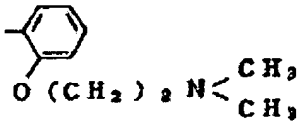
n : 1 X : S
Form of crystals: white powder
Recrystallization solvent: ethanol - water
Melting point: 199.5-201.5°C
Form: $(COOH)_2$

Embodiment 46
Structure
R^1 : 5-NO_2

R^2 : 

n : 1 X : S
Form of crystals: pale yellow needles
Recrystallization solvent: ethanol
Melting point: 196-198°C
Form: $(COOH)_2$

Embodiment 47
Structure
R^1 : 6-Cℓ

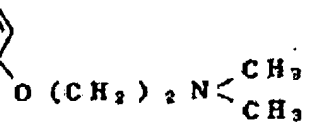
R^2 : 

n : 1 X : S
Form of crystals: white powder
Recrystallization solvent: ethanol - water
Melting point: 179-180°C
Form: free

Embodiment 48

Structure

R^1 : 6-Cℓ

R^2 : 

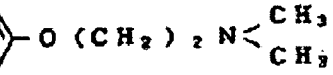
n : 1 X : S

Form of crystals: white powder
Recrystallization solvent: ethanol - water
Melting point: 226.5-228°C (decomposition)
Form: $(COOH)_2$

Embodiment 49

Structure

R^1 : 6-Cℓ

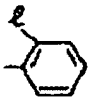
R^2 : 

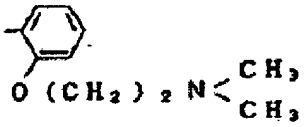
n : 1 X : S

Form of crystals: colorless needles
Recrystallization solvent: dichloromethane - n-hexane
Melting point: 122-123°C
Form: free

Embodiment 50

Structure

R^1 : 6-OCH_2- 

R^2 : 

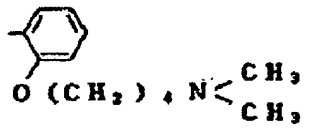
n : 1 X : S

Form of crystals: white powder
Recrystallization solvent: ethanol - water
Melting point: 89.5-91.5°C
Form: free

Embodiment 51

Structure

R^1 : 6-Cℓ

R^2 : 

n : 1 X : S

Form of crystals: pale yellow powder
Recrystallization solvent: ethanol - n-hexane
Melting point: 173-176°C
Form: HCl

Embodiment 52

Structure

R^1 : 6-Cℓ

R^2 : 

$O(CH_2)_2NHCH_3$

n : 1 X : S

Form of crystals: white powder

Recrystallization solvent: ethanol - water

Melting point: 226-227°C (decomposition)

Form: $(COOH)_2$

Embodiment 53

Structure

R^1 : 6-Cℓ

R^2 : 

n : 1 X : S

Form of crystals: colorless needles

Recrystallization solvent: ethanol - water

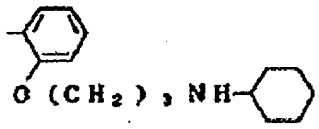
Melting point: 250-252°C (decomposition)

Form: HCl

Embodiment 54

Structure

R^1 : 6-Cℓ

R^2 : 

n : 1 X : S

Form of crystals: colorless needles

Recrystallization solvent: dichloromethane - n-hexane

Melting point: 254-256°C

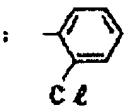
Form: free

/45

Embodiment 55

Structure

R^1 : 6-$O(CH_2)_2N<^{CH_3}_{CH_3}$

R^2 : 

n : 1 X : S

Form of crystals: colorless flakes

Recrystallization solvent: ethanol - water

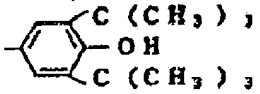
Melting point: 183.5-185°C

Form: $(COOH)_2$

Embodiment 56

Structure

R^1 : —

R^2 : 

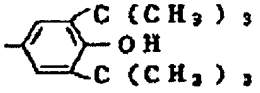
n : 0 X : S

Form of crystals: colorless prisms
Recrystallization solvent: n-hexane
Melting point: 97.5-99.5°C
Form: free

Embodiment 57

Structure

R^1 : 5-OH

R^2 : 

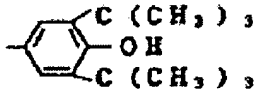
n : 1 X : S

Form of crystals: colorless needles
Recrystallization solvent: n-hexane - ethyl acetate
Melting point: 240°C (decomposition)
Form: free

Embodiment 58

Structure

R^1 : 6-OH

R^2 : 

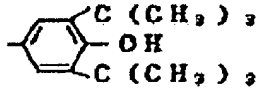
n : 1 X : S

Form of crystals: colorless needles
Recrystallization solvent: n-hexane - ethyl acetate
Melting point: 289-291°C (decomposition)
Form: free

Embodiment 59

Structure

R^1 : 4-OH

R^2 : 

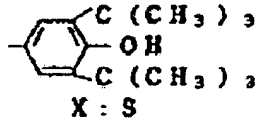
n : 1 X : S

Form of crystals: colorless powder
Recrystallization solvent: n-hexane - ethyl acetate
Melting point: 179-180°C
Form: free

Embodiment 60

Structure

R^1 : 6-OCH_3

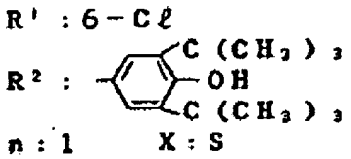
R^2 : 

n : 1 X : S

Form of crystals: colorless needles

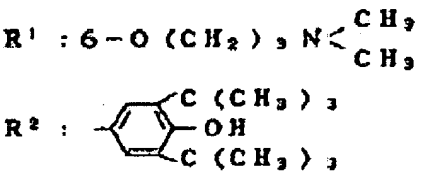
Recrystallization solvent: n-hexane
Melting point: 170.5-171.5°C
Form: free

Embodiment 61
Structure



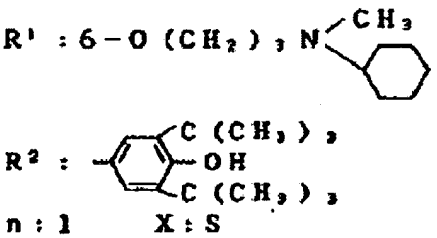
Form of crystals: colorless needles
Recrystallization solvent: n-hexane - ethyl acetate
Melting point: 163.5-164°C
Form: free

Embodiment 62
Structure



Form of crystals: white powder
Recrystallization solvent: ethyl acetate - n-hexane
Melting point: 205-220°C
NMR analysis results: 8)
Form: free

Embodiment 63
Structure



Form of crystals: pale yellow, undefined
NMR analysis results: 9)
Form: free

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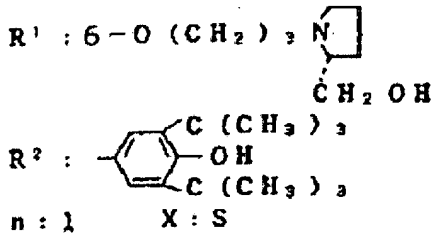
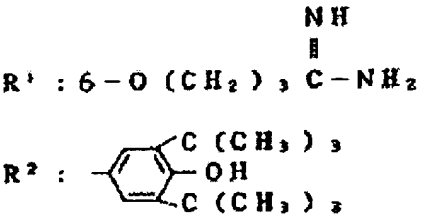
Embodiment 64
Structure



n : 1 X : S

Form of crystals: pale yellow, undetermined
NMR analysis results: 10)
Form: free

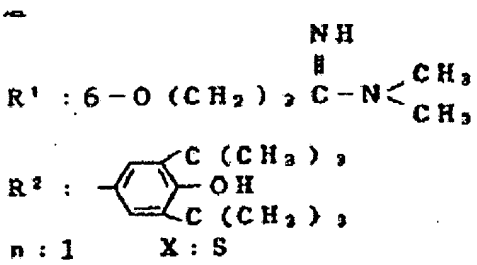
Embodiment 65
Structure



n : 1 X : S

Form of crystals: pale green needles
Recrystallization solvent: 2-propanol - diethylether
Melting point: 185-187°C
Form: HCl

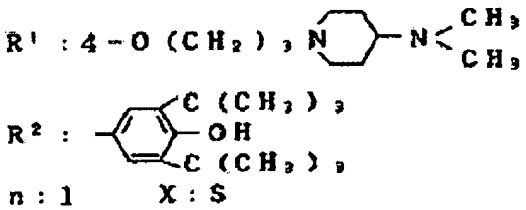
Embodiment 66
Structure



n : 1 X : S

Form of crystals: pale green powder
Recrystallization solvent: 2-propanol - diethylether
Melting point 247-250°C
Form: HCl

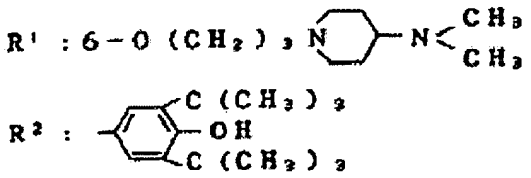
Embodiment 67
Structure



n : 1 X : S

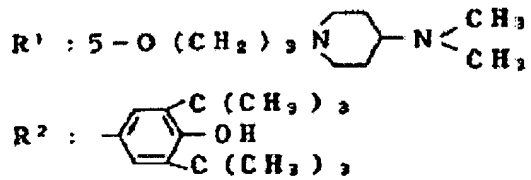
Form of crystals: yellow powder
Recrystallization solvent: dichloromethane - n-hexane
Melting point: 104-106°C
Form: free

Embodiment 68
Structure



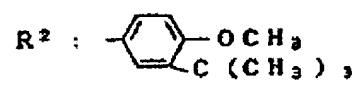
n : 1 X : S
Form of crystals: white powder
Melting point: 136-137°C
NMR analysis results: 11)
Form: free

Embodiment 69
Structure



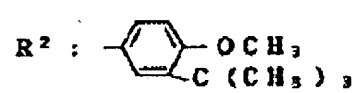
n : 1 X : S
Form of crystals: yellow powder
Recrystallization solvent: dichloromethane - n-hexane
Melting point: 163-164°C
Form: free

Embodiment 70
Structure



n : 0 X : S
Form of crystals: colorless flakes
Recrystallization solvent: n-hexane
Melting point: 58-61°C
Form: free

Embodiment 71
Structure

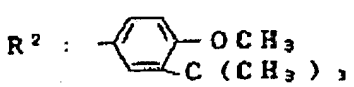


n : 1 X : S
Form of crystals: yellow needles
Recrystallization solvent: ethyl acetate - n-hexane
Melting point: 147-148°C
Form: free

/47

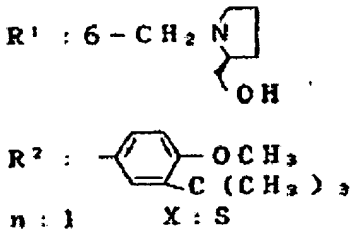
Embodiment 72

Structure



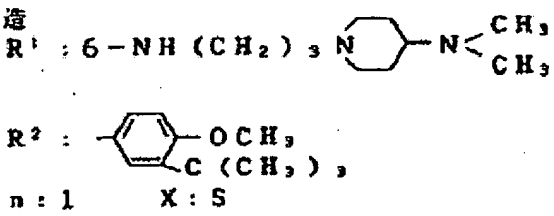
Form of crystals: colorless powder
Recrystallization solvent: ethyl acetate - n-hexane
Melting point: 150-151°C
Form: free

Embodiment 73
Structure



Form of crystals: colorless needles
Recrystallization solvent: n-hexane
Melting point: 134-135°C
Form: free

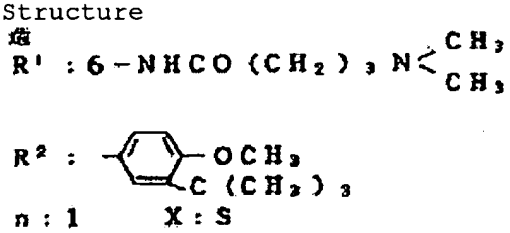
Embodiment 74
Structure



Form of crystals: pale yellow powder
Recrystallization solvent: ethanol
Melting point: 185-187°C

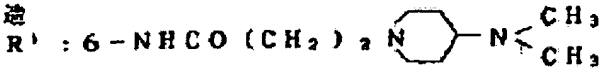
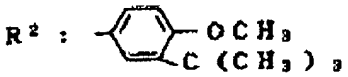
Form:

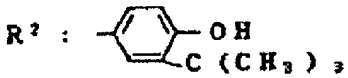
Embodiment 75
Structure

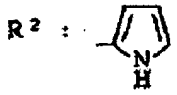


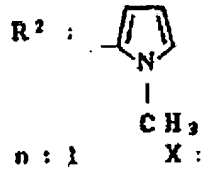
Form of crystals: colorless powder
Recrystallization solvent: dichloromethane - n-hexane
Melting point: 85-87°C

Form: free

Embodiment 76
Structure


n : 1 X : S
Form of crystals: colorless powder
Recrystallization solvent: ethyl acetate - n-hexane
Melting point: 101-103°C
Form: free

Embodiment 77
Structure
R^1 : —

n : 0 X : S
Form of crystals: pale yellow needles
Recrystallization solvent: ethyl acetate - n-hexane
Melting point: 189-192°C (decomposition)
Form: free

Embodiment 78
Structure
R^1 : 6-OH

n : 1 X : S
Form of crystals: colorless needles
Recrystallization solvent: ethanol - water
Melting point: 238-241°C (decomposition)
Form: free

Embodiment 79
Structure
R^1 : 6-OH

n : 1 X : S
Form of crystals: colorless needles
Recrystallization solvent: methanol - water
Melting point: 177.5-178.5°C (decomposition)
Form: free

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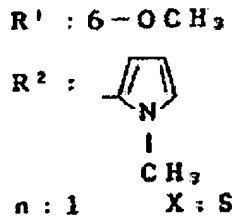
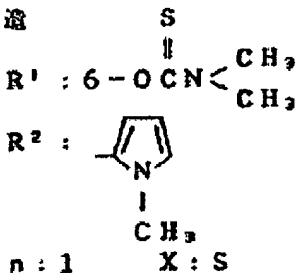
Embodiment 80
Structure



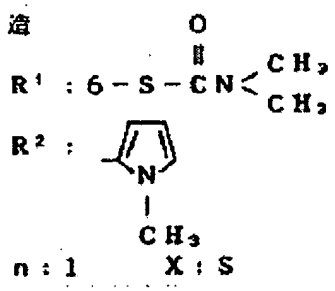
Form of crystals: pale yellow needles
Recrystallization solvent: n-hexane
Melting point: 91-92°C
Form: free

Embodiment 81
Structure



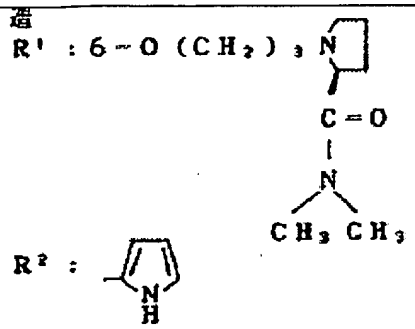
Form of crystals: colorless powder
Recrystallization solvent: ethyl acetate - diethylether
Melting point: 157-158°C
Form: free

Embodiment 82
Structure



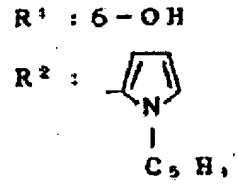
Form of crystals: colorless powder
Recrystallization solvent: ethyl acetate -diethylether
Form: free

Embodiment 83
Structure



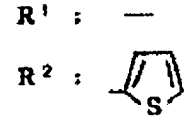
n : 1 X : S
Form of crystals: pale yellow, indefinite
NMR analysis results: 12)
Form: free

Embodiment 84
Structure



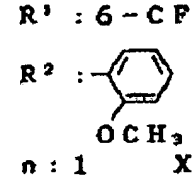
n : 1 X : S
Form of crystals: colorless needles
Recrystallization solvent: n-hexane - diethylether
Melting point: 60-61°C
Form: free

Embodiment 85
Structure



n : 0 X : S
Form of crystals: colorless needles
Recrystallization solvent: dichloromethane - n-hexane
Melting point: 97.5-98°C
Form: free

Embodiment 86
Structure



n : 1 X : NH
Form of crystals: white powder
Recrystallization solvent: ethyl acetate - n-hexane
Melting point: 205-206.5°C
Form: free

Embodiment 87

Structure

R^1 : 6-Cl

R^2 : 

n : 1 X : NH

Form of crystals: pale yellow needles
Recrystallization solvent: 2-propanol - water
Melting point: 203-204°C
Form: free

/49

Embodiment 88

Structure

R^1 : 6-CF_3

R^2 : 

n : 1 X : NH

Form of crystals: white powder
Recrystallization solvent: dichloromethane - n-hexane
Melting point: 91.5-92.0°C
Form: free

Embodiment 89

Structure

R^1 : 6-CF_3

R^2 : 

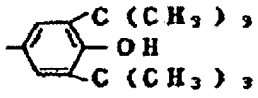
n : 1 X : NH

Form of crystals: white powder
Recrystallization solvent: diethylether - n-hexane
Melting point: 264.5-265.5°C
Form: free

Embodiment 90

Structure

R^1 : 6-Cl

R^2 : 

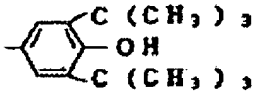
n : 1 X : NH

Form of crystals: white flakes
Recrystallization solvent: dichloromethane - methanol
Melting point: 286-292°C (decomposition)
NMR analysis results: 13)
Form: free

Embodiment 91

Structure

R^1 : 6-Cℓ

R^2 : 

n : 1 X : N
|
C_2H_5

Form of crystals: colorless needles
Recrystallization solvent: dichloromethane - n-hexane
Melting point: 235-235.5°C
Form: free

Embodiment 92
Structure
R^1 : 6-Cℓ

R^2 : $-CH_2S$ 

n : 1 X : NH
Form of crystals: colorless powder
Recrystallization solvent: isopropyl alcohol
Melting point: 184.5-194.5°C (decomposition)
Form: HCl

Embodiment 93
Structure
R^1 : 6-CF_3

R^2 : 

n : 1 X : NH
Form of crystals: colorless needles
Recrystallization solvent: dichloromethane - n-hexane
Melting point: 191.5-192.5°C
Form: free

Embodiment 94
Structure
R^1 : 6-Cℓ

R^2 : 

n : 1 X : NH
Form of crystals: pale yellow flakes
Recrystallization solvent: dichloromethane - n-hexane
Melting point: 226-229°C
Form: free

Embodiment 95
Structure

R^1 : 6-Cℓ

R^2 : 

n : 1 X : NH
Form of crystals: pale brown powder
Recrystallization solvent: dichloromethane - n-hexane
Melting point: 237-238°C
Form: free

/50

Embodiment 96
Structure
R^1 : 6-Br

R^2 : 

n : 1 X : NH
Form of crystals: colorless powder
Recrystallization solvent: dichloromethane - n-hexane
Melting point: 149-150°C
Form: free

Embodiment 97
Structure
通
R^1 : 6- 

R^2 : 

n : 1 X : NH
Form of crystals: colorless powder
Recrystallization solvent: dichloromethane - n-hexane
Melting point: 230°C (decomposition)
NMR analysis results: 14)
Form: free

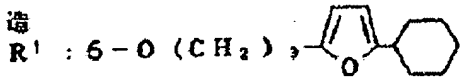
Embodiment 98
Structure
通
R^1 : 6- 

R^2 : 

n : 1 X : NH
Form of crystals: colorless powder
Recrystallization solvent: dichloromethane - diethylether
Melting point: 171-172°C
Form: free

Embodiment 99

Structure

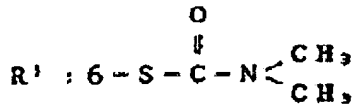


n : 1 X : NH

Form of crystals: pale yellow powder
Recrystallization solvent: dichloromethane - diethylether
Melting point: 150-151°C
Form: free

Embodiment 100

Structure

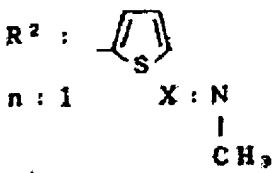


n : 1 X : NH

Form of crystals: pale brown powder
Recrystallization solvent: ethanol - n-hexane
Melting point: 241-243°C
Form: free

Embodiment 101

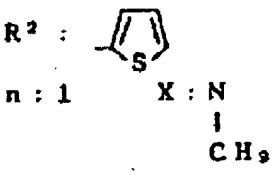
Structure



Form of crystals: colorless powder
Recrystallization solvent: diethylether - n-hexane
Melting point: 145°C (sublimation)
Form: free

Embodiment 102

Structure



Form of crystals: pale yellow powder
Recrystallization solvent: dichloromethane - n-hexane
Melting point: 129-130°C
Form: free

Embodiment 103
Structure

R^1 : 6-Cl

R^2 : 

n : 1 X : N-CH_3

Form of crystals: pale yellow flakes
Recrystallization solvent: isopropyl alcohol - water
Melting point: 156.5-159.5°C
Form: free

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Embodiment 104
Structure

R^1 : 6-CF_3

R^2 : 

n : 1 X : N-$CH_2CH=CH_2$

Form of crystals: colorless powder
Recrystallization solvent: n-hexane
Melting point: 102-103°C
Form: free

Embodiment 105
Structure

R^1 : 5-CF_3

R^2 : 

n : 1 X : N-$CH_2CH=CH_2$

Form of crystals: colorless powder
Recrystallization solvent: n-hexane
Melting point: 67-68°C
Form: free

Embodiment 106
Structure

R^1 : 5-CF_3

R^2 : 

n : 1 X : N-C_5H_{11}

Form of crystals: colorless needles
Recrystallization solvent: diethylether - methanol
Melting point: 97-99°C

Form: HCl

Embodiment 107

Structure

R^1 : 6-CF_3

R^2 : 

n : 1 X : N-C_5H_{11}

Form of crystals: colorless needles

Recrystallization solvent: methanol - diethylether

Melting point: 91-93°C

Form: HCl

Embodiment 108

Structure

R^1 : 6-Cℓ

R^2 : 

n : 1 X : N-CH_2- 

Form of crystals: pale yellow needles

Recrystallization solvent: dichloromethane - n-hexane

Melting point: 154.5-157.5°C

Form: free

Embodiment 109

Structure

R^1 : 6-NO_2

R^2 : 

n : 1 X : S

Form of crystals: pale yellow needles

Recrystallization solvent: ethanol

Melting point: 193-195°C

Form: free

Embodiment 110

Structure

R^1 : 6-NH_2

R^2 : 

n : 1 X : S

Form of crystals: pale yellow flakes

Recrystallization solvent: ethyl acetate - n-hexane

Melting point: 185.5-185°C

Form: free

Embodiment 111
Structure
R^1 : 6-$NHCOCH_3$

R^2 : 

n : 1 X : S
Form of crystals: pale yellow needles
Recrystallization solvent: ethanol
Melting point: 231-232°C
Form: free

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Embodiment 112
Structure
R^1 : 6-$O(CH_2)_3Cl$

R^2 : 

n : 1 X : S
Form of crystals: white powder
NMR analysis results: 15)
Form: free

Embodiment 113
Structure
R^1 : 6-NHC_2H_5

R^2 : 

n : 1 X : S
Form of crystals: yellow needles
Recrystallization solvent: methylene chloride - n-hexane
Melting point: 146.5-147.5°C
Form: free

Embodiment 114
Structure
R^1 : 6-CN

R^2 : 

n : 1 X : S
Form of crystals: pale yellow needles
Recrystallization solvent: ethanol
Melting point: 197.5-198.5°C
Form: free

Embodiment 115
Structure

R^1 : 6-OH

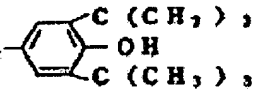
R^2 : 

n : 1 X : S

Form of crystals: pale yellow prisms
Recrystallization solvent: ethanol - water
Melting point: 190-195°C
Form: free

Embodiment 116
Structure

R^1 : 6-OH

7-CH_2- 

R^2 : 

n : 1 X : S

Form of crystals: pale yellow flakes
Recrystallization solvent: ethyl acetate - n-hexane
Melting point: 225-226.5°C
Form: free

Embodiment 117
Structure

R^1 : 6-Cℓ

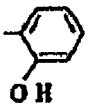
R^2 : 

n : 1 X : S

Form of crystals: colorless needles
Recrystallization solvent: methylene chloride - n-hexane
Melting point: 110.5-111°C
Form: free

Embodiment 118
Structure

R^1 : 6-Cℓ

R^2 : 

n : 1 X : S

Form of crystals: colorless flakes
Recrystallization solvent: chloroform
Melting point: 195-196°C
Form: free

Embodiment 119
Structure

R^1 : 6-Cℓ

R^2 : 

O $(CH_2)_2$ Cℓ

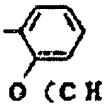
n : 1 X : S

Form of crystals: colorless needles
Recrystallization solvent: methylene chloride - n-hexane
NMR analysis results: 16)
Form: free

/53

Embodiment 120
Structure

R^1 : 6-OC_2H_5

R^2 : 

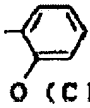
O $(CH_2)_2$ N$\begin{matrix}CH_3\\CH_3\end{matrix}$

n : 1 X : S

Form of crystals: yellow powder
Recrystallization solvent: ethanol
Melting point: 234-236°C (decomposition)
Form: HCl

Embodiment 121
Structure

R^1 : 6-OH

R^2 : 

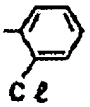
O $(CH_2)_2$ N$\begin{matrix}CH_3\\CH_3\end{matrix}$

n : 1 X : S

Form of crystals: yellow powder
Recrystallization solvent: ethanol
Melting point: 235-236°C
Form: HCl

Embodiment 122
Structure

R^1 : 6-OH

R^2 : 

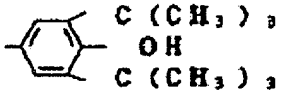
Cℓ

n : 1 X : S

Form of crystals: colorless needles
Recrystallization solvent: isopropyl alcohol
Melting point: 208-209°C
Form: free

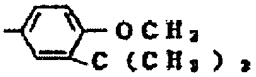
Embodiment 123
Structure

R^1 : 6-$O(CH_2)_3CN$

R^2 : 

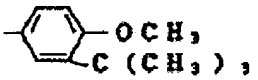
n : 1 X : S
Form of crystals: colorless needles
Recrystallization solvent: n-hexane - ethyl acetate
Melting point: 135-137°C
Form: free

Embodiment 124
Structure
R^1 : 6-CN

R^2 : 

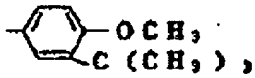
n : 1 X : S
Form of crystals: colorless needles
Recrystallization solvent: ethanol
Melting point: 164-165°C
Form: free

Embodiment 125
Structure
R^1 : 6-CHO

R^2 : 

n : 1 X : S
Form of crystals: pale yellow powder
Recrystallization solvent: ethyl acetate - n-hexane
Melting point: 161-162°C
Form: free

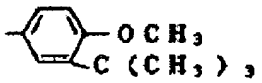
Embodiment 126
Structure
R^1 : 6-NO_2

R^2 : 

n : 1 X : S
Form of crystals: yellow needles
Recrystallization solvent: ethanol
Melting point: 202-203°C
Form: free

Embodiment 127
Structure

R^1 : 6-NH$(CH_2)_3Cl$

R^2 : 

n : 1 X : S
Form of crystals: pale brown oily substance
NMR analysis results: 17)
Form: free

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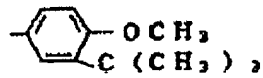
Embodiment 128
Structure
R^1 : 6-NHCO$(CH_2)_2Cl$

R^2 : 

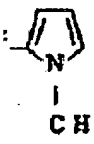
n : 1 X : S
Form of crystals: pale yellow powder
NMR analysis results: 18)
Form: free

Embodiment 129
Structure
R^1 : 6-OC_2H_5

R^2 : 

n : 1 X : S
Form of crystals: pale brown prisms
Recrystallization solvent: ethanol
Melting point: 142.5-143.5°C
Form: free

Embodiment 130
Structure
R^1 : 6-OC_2H_5

R^2 : 

n : 1 X : S
Form of crystals: colorless needles
Recrystallization solvent: n-hexane
Melting point: 87-88°C
Form: free

Embodiment 131
Structure

R^1 : 6-NH_2

R^2 : 

n : 1 X : NH
Form of crystals: pale yellow powder
Recrystallization solvent: methanol - diethylether
Melting point: 170°C or greater (decomposition)
NMR analysis results: 19)
Form: 2HCl

Embodiment 132
Structure
R^1 : 6-OCH_3

R^2 : 

n : 1 X : NH
Form of crystals: pale yellow flakes
Recrystallization solvent: chloroform - petroleum ether
Melting point: 82-85°C
Form: free

Embodiment 133
Structure
R^1 : 6-OH

R^2 : 

n : 1 X : NH
Form of crystals: pale yellow powder
Recrystallization solvent: ethanol - n-hexane
Melting point: 202-205°C
Form: free

Embodiment 134
Structure
R^1 : 6-$OCN<^{CH_3}_{CH_3}$

R^2 : 

n : 1 X : NH
Form of crystals: pale yellow powder
Recrystallization solvent: chloroform - diethylether
Melting point: 113-117°C
Form: free

Embodiment 135
Structure

R^1 : 6-OC_2H_5

R^2 : 

n : 1 X : S

Form of crystals: white powder
Recrystallization solvent: ethyl acetate - n-hexane
Melting point: 103-104°C
Form: free

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Table 3

1	NMR (DMSO-d_6) δ値 1.55-1.7 (2H, m) 2.0-2.2 (2H, m) 3.15-3.4 (2H, m) 4.1-4.2 (2H, m) 7.32 (1H, d-d, J=2.2Hz, 8.6 Hz) 7.46 (1H, d, J=8.6Hz) 7.92 (1H, d, J=2.1Hz)
2	NMR (DMSO-d_6) δ値 1.55-1.80 (2H, m) 2.00-2.20 (2H, m) 3.20-3.60 (3H, m) 4.00-4.20 (2H, m) 7.12 (1H, d-d, J=2.8.5Hz) 7.50 (1H, d, J=2Hz) 7.82 (1H, d, J=8.5Hz) 8.51 (2H, br-s)
3	NMR (DMSO-d_6) δ値 1.60-1.80 (2H, m) 2.10-2.30 (2H, m) 3.30-3.50 (3H, m) 4.10-4.30 (2H, m) 7.21 (1H, d-d, J=1.7.8Hz) 7.36 (1H, d-d, J=8.7.8Hz) 7.47 (1H, d-d, J=1.1.8Hz) 8.50 (3H, br-s)

[(top line of each section) δ value]

4	NMR (DMSO-d_6) δ値 1.52-1.78 (2H, m) 2.00-2.20 (2H, m) 3.13-3.52 (3H, m) 4.00-4.23 (2H, m) 7.50 (1H, d, J=2Hz) 7.95 (1H, d, J=2Hz) 8.05-8.48 (3H, m)
5	NMR ($CDC\ell_3$) δ値 7.30-7.65 (6H, m) 7.68 (1H, s)
6	NMR (DMSO-d_6) δ値 7.40 (1H, d, J=2Hz) 7.80 (1H, d, J=2Hz) 8.00 (2H, s)
7	NMR (DMSO-d_6) δ値 1.85-2.05 (2H, m) 2.2-2.4 (2H, m) 2.80 (3H, s) 2.82 (3H, s) 3.5-3.65 (2H, m) 3.74 (1H, m) 4.2-4.3 (2H, m) 7.00 (1H, d-d, J=2.3, 8.8Hz) 7.46 (1H, d, J=2.3Hz) 7.52 (1H, d, J=8.8Hz)

[(top line of each section) δ value]

8	NMR ($CDCl_3$) δ値 1. 51 (18H, s) 2. 35-2. 52 (2H, m) 2. 89 (6H, s) 3. 23-3. 38 (2H, m) 4. 17 (2H, t, J=5. 5Hz) 5. 55 (1H, s) 7. 01 (1H, d-d, J=9, 2. 5Hz) 7. 31 (1H, d, J=2. 5Hz) 7. 85 (2H, s) 7. 91 (1H, d, J=9Hz)
9	NMR ($CDCl_3$) δ値 1. 00-1. 45 (5H, m) 1. 51 (18H, s) 1. 70 (1H, m) 1. 85-1. 95 (2H, m) 2. 07-2. 17 (2H, m) 2. 24-2. 40 (2H, m) 2. 59 (3H, s) 2. 90 (1H, m) 2. 97-3. 10 (2H, m) 4. 13 (2H, t, J=6Hz) 5. 54 (1H, s) 7. 02 (1H, d-d, J=9, 2. 5Hz) 7. 32 (1H, d, J=2. 5Hz) 7. 85 (2H, s) 7. 89 (1H, d, J=9Hz)

[(top line of each section) δ value]

10	NMR (CDCℓ$_3$) δ値 1. 51 (18H, s) 1. 80-2. 05 (4H, m) 2. 10-2. 27 (2H, m) 2. 50 (1H, m) 、2. 70 (1H, m) 2. 92 (1H, m) 3. 18 (1H, m) 3. 45 (1H, m) 3. 58 (1H, m) 3. 78 (1H, m) 4. 13 (2H, t, J=6Hz) 5. 55 (1H, s) 7. 05 (1H, d-d, J=9, 2. 5Hz) 7. 32 (1H, d, J=2. 5Hz) 7. 85 (2H, s) 7. 90 (1H, d, J=9Hz)
11	NMR (CDCℓ$_3$) δ値 1. 51 (18H, s) 1. 50-1. 70 (2H, m) 1. 75-2. 10 (6H, m) 2. 16-2. 44 (1H, m) 2. 33 (6H, s) 2. 50-2. 62 (2H, m) 3. 00-3. 13 (2H, m) 4. 08 (2H, t, J=6. 5Hz) 5. 53 (1H, s) 7. 04 (1H, d-d, J=9, 2. 5Hz) 7. 33 (1H, d, J=2. 5Hz) 7. 85 (2H, s) 7. 89 (1H, d, J=9Hz)

[(top line of each section) δ value]

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12	NMR (CDCℓ$_3$) δ値 1. 75-2. 25 (6H, m) 2. 32 (1H, m) 2. 52 (1H, m) 2. 85 (1H, m) 2. 94 (3H, s) 3. 07 (3H, s) 3. 22-3. 42 (2H, m) 3. 98-4. 18 (2H, m) 6. 30 (1H, m) 6. 78 (1H, m) 6. 94 (1H, m) 7. 02 (1H, d-d, J=9, 2. 5Hz) 7. 31 (1H, d, J=2. 5Hz) 7. 74 (1H, d, J=9Hz)
13	NMR (DMSO-d$_6$) δ値 1. 48 (18H, s) 7. 19 (1H, br-d, J=9Hz) 7. 46 (1H, s) 7. 40-7. 80 (2H, m) 7. 96 (2H, s) 12. 88 (1H, m)
14	NMR (CDCℓ$_3$) δ値 1. 94-2. 14 (4H, m) 3. 32-3. 40 (4H, m) 6. 50-6. 70 (2H, m) 7. 09 (1H, d-d, J=4. 5Hz) 7. 37 (1H, d, J=4Hz) 7. 47-7. 57 (2H, m)

[(top line of each section) δ value]

15	NMR (CDCℓ$_3$) δ値 2. 29 (2H, m) 3. 78 (2H, t, J=6Hz) 4. 05 (3H, s) 4. 20 (2H, t, J=6Hz) 7. 00-7. 20 (3H, m) 7. 33-7. 50 (2H, m) 7. 96 (1H, d, J=9Hz) 8. 46 (1H, dd, J=9, 2Hz)
18	NMR (CDCℓ$_3$) δ値 4. 02 (2H, t, J=6Hz) 4. 45 (2H, t, J=6Hz) 7. 00 (1H, d, J=8Hz) 7. 16 (1H, m) 7. 38-7. 55 (2H, m) 7. 90 (1H, d, J=2Hz) 7. 97 (1H, d, J=8. 7Hz) 8. 53 (1H, d-d, J=1. 7, 8Hz)
17	NMR (CDCℓ$_3$) δ値 1. 44 (9H, s) 2. 13 (2H, m) 3. 41 (2H, t, J=7Hz) 3. 69 (2H, t, J=7Hz) 3. 90 (3H, s) 6. 76 (1H, d-d, J=9. 2Hz) 6. 93 (1H, d, J=9Hz) 7. 02 (1H, d, J=2Hz) 7. 78-7. 88 (2H, m) 7. 95 (1H, d, J=2Hz)

[(top line of each section) δ value]

18	NMR (CDCℓ$_3$) δ値 1. 42 (9H, s) 2. 90 (2H, t, J=6Hz) 3. 93 (3H, s) 3. 94 (2H, t, J=6Hz) 7. 18 (1H, d, J=9Hz) 7. 60 (1H, d-d, J=9. 2Hz) 7. 83-8. 03 (3H, m) 8. 52 (1H, s)
19	NMR (DMSO-d$_6$) δ値 7. 24-7. 50 (2H, m) 7. 71 (1H, s) 7. 77 (1H, d, J=8Hz) 8. 03 (1H, d, J=5Hz) 8. 26 (1H, d, J=4Hz)

[(top line of each section) δ value]

Embodiment 136

A 3 g quantity of 2-aminothiophenol, 4.4 g of 2-carboxythiophene, and 5.1 g of phosphorus pentoxide were added to 40 g of methanesulfonic acid and the mixture was stirred with heating for 8 hours at 70°C under a nitrogen atmosphere. The mixture was poured into ice water and extracted with chloroform. The chloroform layer was washed with water and dried (sodium sulfate). The solvent was distilled off under reduced pressure. The residue was refined by silica gel chromatography (methylene chloride:n-hexane = 1:1) and then recrystallized from methylene chloride-n-hexane, yielding 3.5 g of 2-(2-thienyl)benzthiazole in the form of colorless acicular crystals.

Melting point: 97.5-98°C

Embodiment 137

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Under a nitrogen atmosphere, 4 g of o-anisic acid and 4 g of 3,4-diaminobenzotrifluoride were added to a mixture of 8 g of phosphorus oxide and 80 g of methanesulfonic acid, and the mixture was stirred with heating for 12 hours at 80°C. The mixture was poured into ice water and rendered alkaline with a sodium hydroxide solution. The precipitating crystals were collected by filtration, washed with water, and dried. The crystals were refined by silica gel chromatography (chloroform:ethyl acetate:n-hexane = 1:1:1) and recrystallized from ethyl acetate-n-hexane, yielding 4.3 g of 2-(2-methoxyphenyl)-6-trifluoromethylbenzimidazole in the form of a white powder.

Melting point: 205-206.5°C

The compounds of above-described Embodiments 33-84 and 87-135 were obtained using suitable starting materials in the same manner as in Embodiments 136 and 137.

Embodiment 138

Under a nitrogen atmosphere, 6.9 g of 2-amino-5-ethoxythiophenol, 3.4 g of 2-formylpyrrole, and 6 g of 4 Angstrom molecular sieve were added to 60 mL of pyridine and the mixture was stirred for 2 days at room temperature. The mixture was poured into ice water and extracted with chloroform. The chloroform layer was washed with water, 5 percent hydrochloric acid aqueous solution, saturate sodium bicarbonate aqueous solution, and saturated brine, and then dried (sodium sulfate). The solvent was then distilled off under reduced pressure. The residue was refined by silica gel chromatography (methyl chloride) and recrystallized from ethanol, yielding 2.1 g of 2-(2-pyrrolyl)-6-ethoxybenzthiazole in the form of light brown prismatic crystals.

Melting point: 142.5-143.5°C

Embodiment 139

A 2 g quantity of 4-chloro-o-phenylenediamine and 1.57 g of 3-thiophene aldehyde were added to 20 mL of ethanol and the mixture was hot refluxed for 6 hours. The mixture was concentrated under reduced pressure. The reside was then refined by silica gel chromatography (chloroform:ethyl acetate:n-hexane = 1:1:1) and recrystallized from methylene chloride-n-hexane, yielding 0.6 g of 2-(3-thienyl)-6-chlorobenzimidazole in the form of a light brown powder.

Melting point: 237-238°C

The compounds of above-described Embodiments 33-94, 96-128, and 130-135 were obtained using suitable starting materials in the same manner as in Embodiments 138 and 139.

Embodiment 140

A 1.48 quantity of 3-bromo-4-(4-methoxy-3-t-butylthiobenzoyl-amino)benzonitrile was dissolved in 15 mL of dimethylformamide, 0.89 g of 1,1,3,3-tetramethylguanidine was added, and the mixture was stirred with heating for 1.5 hours at 100°C. Following concentration under reduced pressure, methanol was added to the residue, and the precipitating crystals were collected by filtration. The crystals were then recrystallized from ethanol, yielding 0.93 g of 2-(4-methoxy-3-t-butylphenyl)-6-cyanobenzthiazole in the form of colorless acicular crystals.

Melting point: 164-165°C

The compounds of above-described Embodiments 33-85, 109-123, 125-130, and 135 were obtained using suitable starting materials in the same manner as in Embodiment 140.

Embodiment 141

A 2.4 g quantity of $SnCl_2 \cdot 2H_2O$ was dissolved in 10 mL of concentrated hydrochloric acid at 50-60°C, and 1 g of 3-nitro-4-(2-thenoylamino)benzotrifluoride was added at the same temperature. Following hot refluxing for 1 hour, the mixture was cooled and the precipitating crystals were collected by filtration. The crystals obtained were suspended in water and neutralized with saturated sodium bicarbonate aqueous solution. The precipitating crystals were collected by filtration and refined by silica gel chromatography (chloroform:ethyl acetate:n-hexane = 1:1:1). The crystals were then recrystallized from methylene-n-hexane, yielding 0.6 g of 2-(2-thienyl)-6-trifluoromethylbenzimidazole in the form of colorless acicular crystals.

Melting point: 191.5-192.5°C

The compounds of above-described Embodiments 34, 86-92, 94-108, and 131-134 were obtained using suitable starting materials in the same manner as in Embodiment 141.

Embodiment 142

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A 1 g quantity of 2-chloromethyl-6-chlorobenzimidazole, 0.72 g of 2-mercaptopyridine, and 0.83 g of potassium carbonate were added to 30 mL of acetone and the mixture was hot refluxed for 0.5 hour. Following concentration under reduced pressure, water was added to the residue and the mixture was extracted with chloroform. The chloroform layer was washed with 1 N sodium hydroxide solution and water, and then dried (sodium sulfate). The solvent was then distilled off under reduced pressure. The residue was refined by silica gel chromatography (chloroform:ethyl acetate:n-hexane = 1:1:1). Hydrochloric acid/methanol were added to obtain a hydrochloride. The product was then recrystallized from isopropanol, yielding 0.65 g of 2-(2-pyridylmercaptomethyl)-6-chlorobenzimidazole hydrochloride in the form of a white powder.

Melting point: 184.5-194.5 (decomposition)

NMR: δ (DMSO-d_6):

4.97 (2 H, s)
7.20 (1 H, m)
7.52 (1 H, br-d, J = 8 Hz)
7.57 (1 H, d-d, J=2, 8.5 Hz)
7.75 (1 H, m)
7.82 (1 H, d, J = 8.5 Hz)
7.90 (1 H, d, J = 2 Hz)
8.46 (1 H, m)

Embodiment 143

A 1 g quantity of 2-(4-dimethylaminopiperidinyl)-6-hydroxybenzthiazole bromate, 0.5 g of o-chlorobenzylchloride, and 1 g of DBU were added to 30 mL of isopropyl alcohol and the mixture was hot refluxed for 8 hours. Following concentration under reduced pressure, water was added to the residue and the residue was extracted with chloroform. The chloroform layer was washed with water and dried (sodium sulfate). The solvent was distilled off under reduced pressure. The residue was refined by silica gel chromatography (methylene chloride:methanol - 20:1 -> 8:1), hydrochloric acid was added, and the mixture was solidified under reduced pressure. The mixture was recrystallized from wet isopropyl alcohol, yielding 0.12 g of 2-(4-dimethylaminopiperidinyl)-6-(o-chlorobenzyloxy)benzthiazole hydrochloride in the form of a white power.

Melting point: 244-245°C

Embodiment 144

A 0.49 g quantity of sodium hydride (60 percent oil) was added under a nitrogen atmosphere to a dimethylformamide solution (20 mL) of 2.2 g of 2-(2-thienyl)-6-hydroxybenzimidazole and the mixture was stirred for 2 hours at room temperature. A 1.5 g quantity of dimethylthiocarbamoylchloride was added with ice cooling and the mixture was stirred overnight at room temperature. The mixture was poured into ice water and the precipitating crystals were collected by filtration, dried, and refined by silica gel chromatography (methylene chloride:methanol = 20:1). The crystals were then recrystallized from chloroform-diethylether, yielding 0.7 g of 2-(2-thienyl)-6-(dimethylthiocarbamoyloxy)benzimidazole in the form of a pale yellow powder.

Melting point: 113-117°C

The compounds of above-described Embodiments 11, 18, 19, 20, 29, 30, 33, 34, 38, 39, 40, 41, 50, 55, 60, 62-69, 80, 81, 82, 83, 99, 120, 129, 130, 132, and 135 were obtained using suitable starting materials in the same manner as in Embodiments 143 and 147.

Embodiment 145

A 4 g quantity of 2-(2-methoxyphenyl)-6-hydroxybenzthiazole, 4.9 g of 1-bromo-3-chloropropane, and 4.7 g of DBU were added to 100 mL of isopropyl alcohol and the mixture was hot refluxed for 12 hours. Following concentration under reduced pressure, water was added to the residue and the mixture was extracted with chloroform. The chloroform layer was washed with 5 percent sodium hydroxide and water, and then dried (sodium sulfate). The solvent was then distilled off under reduced pressure. The residue was refined by silica gel chromatography (methylene chloride:n-hexane = 1:), yielding 3 g of 2-2(methoxyphenyl)-6-(3-chloropropoxy)benzthiazole in the form of a white powder.

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NMR: δ ($CDCl_3$):

2.29 (2 H, m)
3.78 (2 H, t, J = 6 Hz)
4.05 (3 H, s)
4.20 (2 H, t, J = 6 Hz)
7.00-7.20 (3 H, m)
7.33-7.50 (2 H, m)
7.96 (1 H, d, J = 9 Hz)
8.46 (1 H, dd, J = 9 Hz, 2 Hz)

Embodiment 146

A 0.5 g quantity of 2-(2-methoxyphenyl)-6-(3-chloropropoxy)benzthiazole and 1 g of sodium iodide were added to 10 mL of acetone and the mixture was hot refluxed for 1 hour. A 1 g quantity of potassium carbonate and 0.8 g of diethanolamine were added and the mixture was hot refluxed for another 40 hours. Following concentration under reduced pressure, water was added to the residue and the mixture was extracted with chloroform. The chloroform layer was washed with water and dried (sodium sulfate). The solvent was distilled off under reduced pressure. The residue was refined by silica gel chromatography (methylene chloride:methanol = 10:1) and then recrystallized from n-hexane-ether, yielding 150 mg of 2-(2-methoxyphenyl)-6-(N,N-diethanolaminopropoxy)benzimidazole in the form of colorless prismatic crystals.

Melting point: 83-85.5°C

The compounds of Embodiments 36, 38, 39, 41, 55, 62-64, 67, 68, 69, and 83 were obtained using suitable starting materials in the same manner as in Embodiment 146.

Embodiment 147

A 0.12 g quantity of sodium hydride (60 percent oil) was added under a nitrogen atmosphere to a dimethylformamide solution (15 mL) of 0.64 g of 2-(4-dimethylaminopiperidinyl)-5-amino-6-ethoxybenzthiazole and the mixture was stirred for 15 minutes at room temperature. Following the dropwise addition of 0.38 g of o-chlorobenzylchloride, the mixture was stirred for 24 hours at room temperature. Following concentration under reduced pressure, water was added to the residue and the mixture was extracted with chloroform. The chloroform layer was washed with water and dried (sodium sulfate). The solvent was distilled off under reduced pressure. The residue was refined by silica gel chromatography (chloroform:methanol = 15:1) and recrystallized from ethyl acetate-n-hexane, yielding 0.07 g of 2-(4-dimethylaminopiperidinyl)-5-(o-chlorobenzylamino)-6-ethoxybenzthiazole in the form of pale orange acicular crystals.

Melting point: 158.5-161.5°C

The compounds of Embodiments 2, 4, 12, 14-23, 26, 28-32, 36, 37, 38, 41, 55, 62, 63, 74, and 113 were obtained using suitable starting materials in the same manner as in Embodiment 147.

Embodiment 148

A 1.7 g quantity of 2-(4-dimethylaminopiperidino)-4-amino-6-hydroxybenzthiazole was added to 30 mL of ethanol, 1.5 mL of acetic anhydride was added, and the mixture was stirred overnight at room temperature. Following concentration under reduced pressure, 2 g of potassium carbonate was added, 50 mL of methanol was added, and the mixture was stirred for 2 hours at room temperature. The potassium carbonate was filtered off and the mixture was concentrated and dissolved in water. The pH was adjust to about 8 to 9 with acetic acid and the precipitating crystals were collected by filtration. The crystals were recrystallized from wet ethanol, yielding 1.3 g of 2-(4-dimethylaminopiperidino)-4-acetoamido-6-hydroxybenzthiazole in the form of colorless acicular crystals.

Melting point: 230-232°C

The compounds of Embodiments 3, 10, 11, 18, 20, 24-26, 75, 76, and 111 were obtained using suitable starting materials in the same manner as in Embodiment 148.

Embodiment 149

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A 1.1 g quantity of 2-(o-methoxyphenyl)-6-acetoamidobenzthiazole was dissolved in anhydrous tetrahydrofuran, 0.33 g of lithium aluminum hydride was added, and the mixture was hot refluxed for 30 minutes. After cooling, a saturated sodium sulfate aqueous solution was added and the mixture was stirred. Chloroform was then added and the mixture was filtered through cerite. The mother solution was extracted with chloroform. The chloroform layer was washed with water and dried (sodium sulfate). The solvent was distilled off under reduced pressure. The residue was refined by silica gel chromatography (methylene chloride) and recrystallized from methylene chloride-n-hexane, yielding 0.85 g of 2-(o-methoxyphenyl)-6-ethylaminobenzthiazole in the form of yellow acicular crystals.

Melting point: 146.5-147.5°C

The compounds of Embodiments 12, 14-20, 28-32, 36, 37, 41, 55, 62, 63, and 74 were obtained using suitable starting materials in the same manner as in Embodiment 149.

A 0.4 g quantity of 2-(4-methoxy-3-t-butylphenyl)-6-aminobenzthiazole, 2.02 g of 1-bromo-3-chloropropane, and 1.36 g of sodium carbonate were added to 12 mL of ethanol and the mixture was hot refluxed for 10 hours. Following concentration under reduced pressure, water was added to the residue and the mixture was extracted with methylene chloride. The methylene chloride layer was washed with water and dried (sodium sulfate). The solvent was distilled off under reduced pressure. The reside was refined by silica gel chromatography (ethyl acetate:n-hexane = 1:4), yielding 0.4 g of 2-(4-methoxy-3-t-butylphenyl)-6-(3-chloropropylaminobenzthiazole in the form of a light brown oily substance.

NMR: δ ($CDCl_3$):

1.44 (9 H, s)
2.13 (2 H, m)
3.41 (2 H, t, J = 7 Hz)
3.69 (2 H, t, J = 7 Hz)
3.90 (3 H, s)
6.76 (1 H, d-d, J = 9.2 Hz)
6.93 (1 H, d, J = 9 Hz)
7.02 (1 H, d, J = 2 Hz)
7.78-7.88 (2 H, m)
7.95 (1 H, d, J = 2 Hz)

Embodiment 151

A 1 g quantity of 2-(4-methoxy-3-t-butylphenyl)-6-aminobenzthiazole was dissolved in 30 mL of methyl chloride, after which 0.71 g of triethylamine was added. While stirring at room temperature, 0.45 g of 3-chloropropionylchloride was added and the mixture was stirred for 1 hour at the same temperature. Following concentration under reduced pressure, the residue was refined by silica gel chromatography (methylene chloride), yielding 0.58 g of 2-(4-methoxy-3-t-butylphenyl)-6-[(3-chloropropionyl)amino]benzthiazole in the form of a pale yellow powder.

NMR: δ ($CDCl_3$):

1.42 (9 H, s)
2.90 (2 H, t, J = 6 Hz)
3.93 (3 H, s)
3.94 (2 H, t, J = 6 Hz)
7.18 (1 H, d, J = 9 Hz)
7.60 (1 H, d-d, J = 9.2 Hz)
7.83-8.03 (3 H, m)
8.52 (1 H, s)

Embodiment 152

A 0.38 g quantity of 2-(4-methoxy-3-t-butylphenyl)-6-(3-chloropropylamino)benzthiazole, 0.29 g of sodium iodide, and 0.13 g of 4-dimethylaminopiperidine were added to 10 mL of dimethylformamide and the mixture

was stirred with heating for 1 hour at 130°C. Following concentration under reduced pressure, saturated sodium bicarbonate aqueous solution was added to the residue and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and dried (magnesium sulfate). The solvent was removed under reduced pressure. The residue was refined by silica gel chromatography (methylene chloride:methanol:ammonia water = 100:10:1). The mixture was converted to a fumarate in ethanol and recrystallized from ethanol, yielding 0.26 g of 2-(4-methoxy-3-t-butylphenyl)-6-[3-(4-dimethylaminopiperidinyl)propylamino]benzthiazole fumarate in the form of a yellow powder.

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Melting point: 185-187°C

Embodiment 153

A 0.75 g quantity of 2-(4-methoxy-3-t-butylphenyl)-6-[(3-chloropropionyl)amino]benzthiazole, 0.56 g of sodium iodide, and 0.26 g of 4-dimethylaminopiperidine were added to 20 mL of acetonitrile and the mixture was stirred with heating for 3 hours at 50°C. Following concentration under reduced pressure, saturated sodium bicarbonate aqueous solution was added to the residue and the mixture was extracted with methylene chloride. The methylene chloride layer was washed with water and dried (magnesium sulfate). The solvent was removed under reduced pressure. The residue was refined by silica gel chromatography (methylene chloride:methanol:ammonia water = 50:10:1). The mixture was recrystallized from ethyl acetate-n-hexane, yielding 0.40 g of 2-(4-methoxy-3-t-butylphenyl)-6-[3-(4-dimethylaminoperidinyl)propionylamino]benzthiazole fumarate in the form of a white powder.

Melting point: 101-103°C

The compounds of Embodiments 37 and 75 were obtained using suitable starting materials in the same manner as in Embodiments 152 and 153.

Embodiment 154

A 0.92 g quantity of 2-(4-methoxy-3-t-butylphenyl)-6-cyanobenzthiazole was dissolved in 30 mL of toluene and diisobutylaluminumhydride (1.5 N, in toluene) was added dropwise at

-60°C. With completion of the dropwise addition, the mixture was heated over 30 minutes to room temperature. Saturated ammonium chloride aqueous solution was added with ice cooling, the mixture was acidified with 5 percent hydrochloride aqueous solution, and the mixture was extracted with methylene chloride. The methylene chloride layer was washed with water and dried (sodium sulfate). The solvent was distilled off under reduced pressure. The residue was refined by silica gel chromatography (methylene chloride:n-hexane = 5:1) and then refined with ethyl acetate-n-hexane = 5:1, yielding 0.4 g of 2-(4-methoxy-3-t-butylphenyl)-6-formylbenzthiazole in the form of a pale yellow powder.

Melting point: 161-162°C

Embodiment 155

A 0.37 g quantity of 2-(4-methoxy-3-t-butylphenyl)-6-formylbenzthiazole was added to a mixed solvent of 3 mL of methylene chloride and 6 mL of methanol, 43 mg of sodium borohydride was added at room temperature, and the mixture was stirred at room temperature for 1 hour. Concentration was conducted under reduced pressure. Water was added to the residue, and the mixture was extracted with methylene chloride. The methylene chloride layer was washed with water and dried (sodium sulfate). The solvent was distilled off under reduced pressure. The residue was refined by silica gel chromatography (methylene chloride) and then recrystallized from ethyl acetate-n-hexane, yielding 0.25 g of 2-(4-methoxy-3-t-butylphenyl)-6-hydroxymethylbenzthiazole in the form of pale yellow, acicular crystals.

Melting point: 147-148°C

Embodiment 156

A 0.2 g quantity of 2-(4-methoxy-3-t-butylphenyl)-6-hydroxymethylbenzthiazole was added to 6 mL of thionyl chloride and the mixture was stirred for 1 hour at room temperature. Following concentration at reduced pressure, dry chloroform was added and three cycles of azeotropic distillation were conducted. A 60 mg quantity of s-pyrrolinol, 90 mg of DBU, and 6 mL of isopropyl alcohol were added to the residue containing the 2-(4-methoxy-3-t-butylhenyl)-6-chloromethylbenzthiazole obtained and the mixture was hot refluxed for 3 hours. Following concentration under reduced pressure, the residue was refined by silica gel chromatography (methylene chloride:methanol = 20:1). The product was then recrystallized from n-hexane, yielding 0.15 g of 2-(4-methoxy-3-t-butylphenyl)-6-[(2-s-hydroxymethylpyrrolidyl)methyl]benzthiazole in the form of colorless acicular crystals.

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Melting point: 134-135°C

Embodiment 157

A 0.5 g quantity of 2-(o-methoxyphenyl)-6-cyanobenzthiazole was dissolved in 15 mL of anhydrous ethanol and 30 mL of anhydrous chloroform. With ice cooling, the mixture was saturated by blowing in hydrochloride gas and then stirred for 24 hours at 5°C. The mixture was poured into a 5 N sodium hydroxide aqueous solution and extracted with chloroform. The chloroform layer was washed with water and dried (sodium sulfate). The solvent was distilled off under reduced pressure. The residue was dissolved in 15 mL of chloroform, 0.7 g of o-chlorobenzylamine was added, 15 mL of ethanol and 1 mL of hydrochloric acid/ethanol were added, and the mixture was hot refluxed for 4 hours. Following concentration under reduced pressure, a sodium hydroxide aqueous solution was added to the residue, and the mixture was extracted with chloroform. The chloroform layer was washed with water and dried (sodium sulfate). The solvent was distilled off under reduced pressure. The residue was refined by silica gel chromatography (methyl chloride:methanol = 20:1 -> 8:1) and recrystallized from chloroform, yielding 18 mg of 2-(o-methoxyphenyl)-6-[N'-(o-chlorobenzyl)amidino]benzthiazole in the form of a white powder.

Melting point: 275-277°C (decomposition)

Embodiment 158

A 4g quantity of 2-(3,5-di-t-butyl-4-hydroxyphenyl)-6-hydroxybenzthiazole, 2 g of 4-bromobutyronitrile, and 2.1 g of DBU were dissolved in 50 mL of isopropyl alcohol and the mixture was hot refluxed for 5 hours. Following concentration under reduced pressure, water was added to the residue and the mixture was extracted with chloroform. The chloroform layer was washed with water and dried (sodium sulfate). The solvent was distilled off under reduced pressure. The residue was refined by silica gel chromatography (methylene chloride:n-hexane = 3:1) and recrystallized from n-hexane-ethyl acetate, yielding 4.2 g of 2-(3,5-di-t-butyl-4-hydroxyphenyl)-6-(3-cyanopropoxy)benzthiazole in the form of colorless acicular crystals.

Melting point: 135-137°C

Embodiment 159

A 0.55 g quantity of 2-(3,5-di-t-butyl-4-hydroxyphenyl)-6-(3-thoxy-3-iminopropoxy)benzthiazole was dissolved in 30 mL of ethanol, 110 mg of dimethylamine hydrochloride was added, and the mixture was stirred overnight at room temperature. Following concentration under reduced pressure, diethylether was added and the precipitating crystals were collected by filtration. The crystals were recrystallized from isopropyl alcohol-diethylether, yielding 0.5 g of 2-(3,5-di-t-butyl-4-hydroxyphenyl)-6-(3-dimethylamino-3-iminopropoxy)benzthiazole hydrochloride in the form of a pale green powder.

Melting point: 247-250°C

The compound of Embodiment 65 was obtained using suitable starting materials in the same manner as in Embodiment 159.

Embodiment 160

A 0.9 g quantity of 2-(o-methoxyphenyl)-6-hydroxybenzthiazole, 1.1 g of 3,5-di-t-butyl-4-hydroxybenzylchloride, and 1 g of potassium carbonate were added to 20 mL of acetone and the mixture was hot refluxed for 4 hours. Following concentration under reduced pressure, water was added to the residue and the mixture was extracted with chloroform. The chloroform layer was washed with a 5 percent sodium hydroxide aqueous solution and water, and dried (sodium sulfate). The solvent was distilled off under reduced pressure. Methylene chloride-n-hexane was added to the residue and the precipitating crystals were collected by filtration. The crystals were recrystallized from ethyl acetate-n-hexane, yielding 0.7 g of 2-(o-methoxyphenyl)-6-hydroxy-7-(3,5-di-t-butyl-4-hydroxybenzyl)benzthiazole in the form of pale yellow flaky crystals.

Melting point: 225-226.5°C

Embodiment 161

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To 200 mL of diphenylether was added 2-[2-(N-methyl)pyrrolyl]-6-dimethylthiocarbamoyloxybenzthiazole and the mixture was hot refluxed for 2 hours.

After cooling, the reaction solution was refined by silica gel chromatography (methylene chloride). The reaction solution was then recrystallized from ethyl acetate-diethylether = 1:1, yielding 7.04 g of 2-[2-(N-methyl)pyrrolyl]-6-(dimethylcarbamoylthio)benzthiazole in the form of a white powder.

Melting point: 155-156°C

The compound of Embodiment 100 was obtained using suitable starting materials in the same manner as in Embodiment 161.

Embodiment 162

Saturated sodium bicarbonate aqueous solution was added to 240 mg of 2-(2-thienyl)-6-aminobenzimidazole 2 hydrochloride and the mixture was extracted with methylene chloride. The solvent was distilled off under reduced pressure. To the residue were added 110 mg of 2,5-dimethoxytetrahydropyrane and 6 mL of acetic acid and the mixture was stirred with heating for 2 hours at 80°C. After distilling off the acetic acid, saturated sodium bicarbonate aqueous solution was added and the mixture was extracted with methylene chloride. The organic layer was washed with water, dried (magnesium sulfate), and concentrated under reduced pressure. The residue was refined by silica gel chromatography (methylene chloride) and recrystallized from methylene chloride-diethylether, yielding 120 mg of 2-(2-thienyl)-6-(1-pyrrolyl)benzimidazole in the form of a white powder.

Melting point: 171-172°C

Embodiment 163

A 390 mg quantity of 2-(2-thienyl)-6-aminobenzimidazole 2 hydrochloride was added to 12 mL of ethanol, 1.7 g of sodium carbonate and 2.89 g of 1,4-dibromobutane were added, and the mixture was hot refluxed for 1 hour. Following concentration under reduced pressure, water was added to the residue, and the mixture was extracted with methylene chloride. The methylene chloride layer was washed with water and dried (magnesium sulfate). The solvent was distilled off under reduced pressure. The residue was refined by silica gel chromatography (methylene chloride:methanol = 50:1) and recrystallized from methylene chloride:n-hexane, yielding 160 mg of 2-(2-thienyl)-6-(1-pyrrolidinyl)benzimidazole in the form of a white powder.

Melting point: 230°C (decomposition)

NMR: δ ($CDCl_3$):

1.94-2.14 (4 H, m)
3.32-3.40 (4 H, m)
6.50-6.70 (2 H, m)
7.09 (1 H, d-d, J = 4.5 Hz)
7.37 (1 H, d, J = 4 Hz)
7.47-7.57 (2 H, m)

The compound of Embodiment 16 was obtained using suitable starting materials in the same manner as in Embodiment 163.

Embodiment 164

A 0.6 quantity of 2-(2-thienyl)-5-trifluoromethylbenzthiazole was dissolved in 20 mL of DMF, 0.11 g of sodium hydride (60 percent oil) was added, and the mixture was stirred for 20 minutes at room temperature. A 0.48 g quantity of methyl iodide was added dropwise at room temperature, after which the mixture was stirred for 2 hours at 40°C. Following concentration under reduced pressure, water was added to the residue and the mixture was extracted with methylene chloride. The methylene chloride layer was washed with water and dried (magnesium sulfate). The solvent was distilled off under reduced pressure. The residue was refined by silica gel chromatography (methylene chloride:n-hexane = 2:1) and fractionated to Rf values approximately equal to 0.5 and 0.6 (on TLC columns (silica gel:methylene chloride) respectively. The fraction with an Rf approximately equal to 0.5 was recrystallized from diethylether-n-hexane, yielding 80 mg of 1-methyl-2-(2-thienyl)-6-trifluoromethylbenzimidazole in the form of a white powder.

Melting point: 145°C (sublimation)

The fraction with an Rf approximately equal to 0.6 was recrystallized from methylene chloride-n-hexane, yielding 160 mg of 1-methyl-2-(2-thienyl)-5-trifluoromethylbenzimidazole in the form of a pale yellow powder.

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Melting point: 129-130°C

The compounds of Embodiments 91 and 103-108 were obtained using suitable starting materials in the same manner as in Embodiment 164.

Embodiment 165

A 2 g quantity of 2-(2-hydroxyphenyl)-6-chlorobenzthiazole, 1.2 g of N,N-dimethylaminopropylchloride, and 1.6 g of DBU were added to 50 mL of isopropyl alcohol and the mixture was hot refluxed for 3 hours. Following concentration under reduced pressure, water was added to the residue and the mixture was extracted with chloroform. The chloroform layer was washed with water and dried (sodium sulfate). The solvent was distilled off under reduced pressure. The residue was refined by silica gel chromatography (methylene chloride:methanol = 20:1), converted to an oxalate, and recrystallized from wet ethanol, yielding 2 g of 2-(2-dimethylaminopropoxyphenyl)-6-chlorobenzthiazole oxalate in the form of a white powder.

Melting point: 199.5-201.5°C

The compounds of Embodiments 35-44, 46-54, 86-88, 109-117, 120, 121, 124-128, and 135 were obtained using suitable starting materials in the same manner as in Embodiment 165.

Embodiment 166

A 6 g quantity of 2-(2-hydroxyphenyl)-6-chlorobenzthiazole and 4.14 g of potassium carbonate were added to acetonitrile-water = 1:1 (100 mL) and the mixture was hot refluxed for 5 minutes. A 5.8 mL quantity of 1-chloro-2-bromoethane was

added and the mixture was hot refluxed for 10 hours. A 2 g quantity of potassium carbonate and 5.8 g of 1-chloro-2-bromoethane were added and the mixture was hot refluxed for 4 hours. After cooling, the precipitating crystals were collected by filtration and dissolved in chloroform. The chloroform layer was washed with water and dried (sodium sulfate). The solvent was distilled off under reduced pressure. The residue was refined by silica gel chromatography (methylene chloride) and recrystallized from methylene chloride-n-hexane, yielding 5 g of 2-(2-chloroethoxyphenyl)-6-chlorobenzthiazole in the form of colorless acicular crystals.

NMR: δ ($CDCl_3$)

4.02 (2 H, t, J = 6 Hz)
4.25 (2 H, t, J = 6 Hz)
7.00 (1 H, d, J = 8 Hz)
7.16 (1 H, m)
7.38-7.55 (2 H, m)
7.90 (1 H, d, J = 2 Hz)
7.97 (1 H, d, J = 8.7 Hz)
8.53 (1 H, d-d, J = 1.7, 8 Hz)

Embodiment 167

A 1 g quantity of 2-(2-chloroethoxyphenyl)-6-chlorobenzthiazole and 20 mL of methylamine (40 percent solution) were added to 20 mL of ethanol and the mixture was stirred with heating for 5 hours at 70 to 70°C. Following concentration under reduced pressure, water was added to the residue and the mixture was extracted with chloroform. The chloroform layer was washed with water and dried (sodium sulfate). The solvent was distilled off under reduced pressure. The residue was refined by silica gel chromatography (methylene chloride:methanol = 10:1) and converted to an oxalate in acetone. The product was recrystallized from wet ethanol, yielding 0.55 g of 2-(2-methylaminoethoxyphenyl)-6-chlorobenzthiazole oxalate in the form of a white powder.

Melting point: 226.0-227.0°C (decomposition)

The compounds of Embodiments 43-51, 53, 54, 120, and 121 were obtained using suitable starting materials in the same manner as in Embodiment 167.

Embodiment 168

A 2 g quantity of 2-(4-acetoamidepiperidino)-6-chlorobenzthiazole was added to 30 mL of 6 N hydrochloric acid and the mixture was hot refluxed for 5 hours. The reaction solution was concentrated and solidified. The residue was recrystallized from wet ethanol, yielding 1 g of 2-(4-aminopiperidino)-6-chlorobenzthiazole hydrochloride in the form of pale yellow flaky crystals.

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Melting point: 300°C or higher

NMR: δ ($DMSO-d_6$):

1.55-1.7 (2H, m)

2.0-2.2 (2 H, m)
3.15-3.4 (2 H, m)
4.1-4.2 (2 H, m)
7.32 (1 H, d-d, J = 2.2, 8.6 Hz)
7.46 (1 H, d, J = 8.6 Hz)
7.92 (1 H, d, J = 2.1 Hz)

Embodiment 169

A 0.9 g quantity of 2-(4-aminopiperidino)-6-chlorobenzthiazole hydrochloride and 1 mL of 35 percent formalin were added to 98 percent formic acid and the mixture was stirred with heating for 5 hours at 100°C. Following concentration under reduced pressure, water was added to the residue and the mixture was extracted with chloroform. The chloroform layer was washed with water and dried (sodium sulfate). The solvent was distilled off under reduced pressure. The residue was refined by silica gel chromatography (methylene chloride:methanol = 20:1). Hydrochloric acid was added and the mixture was concentrated and solidified. the mixture was then recrystallized from ethanol-n-hexane, yielding 0.71 g of 2-(4-dimethylaminopiperidino)-6-chlorobenzthiazole hydrochloride in the form of a white powder.

Melting point: 285°C (decomposition)

The compounds of Embodiments 12, 15-20, 28-32, 36, 37, 43-52, 55, 62, 63, 67-69, 74, 75, 76, 113, 120, and 121 were obtained using suitable starting materials in the same manner as in Embodiment 169.

Embodiment 170

An 8 g quantity of 2-(4-carbobenzyloxypiperazinyl)-6-nitrobenzthiazole and 23 g of $SnCl_2 \cdot 2H_2O$ were added to 200 mL of anhydrous ethanol and the mixture was stirred with heating for 2 hours at 70-80°C under a nitrogen atmosphere. After cooling, the mixture was poured into water and neutralized with saturated sodium bicarbonate aqueous solution. Chloroform was added and the insoluble matter was filtered out. The aqueous layer was extracted with chloroform. The organic layer was added and the mixture was washed with water and dried (sodium sulfate). Following concentration under reduced pressure, the product was recrystallized from methanol-n-hexane, yielding 5.6 g of 2-(4-carbobenzyloxypiperazinyl)-6-aminobenzthiazole in the form of a gray powder.

Melting point: 126-129°C

Embodiment 171

A 4.6 g quantity of 2-(o-methoxyphenyl)-6-nitrobenzthiazole and 20 g of $SnCl_2 \cdot 2H_2O$ were added to 100 mL of concentrated hydrochloric acid and the mixture was stirred with heating for 1 hour at 80°C. The mixture was poured into ice water, rendered alkaline with sodium hydride, and extracted with chloroform. The chloroform layer was washed with water and dried (sodium sulfate). The solvent was distilled off under reduced pressure. The crude crystals were recrystallized from ethyl acetate-n-hexane, yielding 4 g of 2-(o-methoxyphenyl)-6-aminobenzthiazole in the form of pale yellow flaky crystals.

Melting point: 183.5-185°C

Embodiment 172

A 0.96 g quantity of 2-(4-methoxy-3-t-butylphenyl)-6-nitrobenzthiazole was suspended in 50 mL of acetic acid and 0.3 g of 10 percent palladium carbon was added. After catalytic hydrogenation for 1 hour at 80°C under ordinary pressure, the catalyst was filtered out and the filtrate was concentrated under reduced pressure. Saturated sodium bicarbonate was added and the mixture was extracted with methylene chloride. The methylene chloride layer was washed with water and dried (sodium sulfate). The solvent was distilled off under reduced pressure. The residue was refined by silica gel chromatography (methylene chloride) and recrystallized from ethyl acetate-n-hexane = 1:5, yielding 0.5 g of 2-(4-methoxy-3-t-butylphenyl)-6-aminobenzthiazole in the form of a white powder.

Melting point: 150-151°C

The compounds of Embodiments 29, 30, 31, and 131 were obtained using suitable starting methods in the same manner as in Embodiments 170, 171, and 172.

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Embodiment 173

A 3.4 g quantity of 2-(2-methoxyphenyl)-6-ethoxybenzthiazole was added to 40 mL of 47 percent hydrobromic acid aqueous solution and the mixture was hot refluxed for 4 hours. The mixture was poured into water and the precipitating crystals were collected by filtration. The crystals were recrystallized from wet ethanol, yielding 2.3 g of 2-(2-methoxyphenyl)-6-hydroxybenzthiazole in the form of yellow prismatic crystals.

Melting point: 190-195°C

Embodiment 174

Under a nitrogen atmosphere, n-butanethiole was added to 250 mL of anhydrous hexamethylphosphoryltriamide. While cooling with methanol-ice, 160 mL of n-butyllithium (1.6 N, in n-hexane) was added dropwise. the mixture was stirred for 30 minutes at room temperature, after which 100 mL of an anhydrous hexamethylphosphoryltriamide solution of 35 g of 2-(3,5-di-t-butyl-4-hydroxyphenyl)-6-methoxybenzthiazole was added dropwise. After stirring for 30 minutes at the same temperature, the mixture was stirred with heating for 6 hours at 70-80°C. The mixture was washed with water, saturated sodium bicarbonate aqueous solution, and saturated brine, and then dried (sodium sulfate). The solvent was distilled off under reduced pressure, n-hexane was added to the residue, and crystals were precipitated. The crude crystals were collected by filtration and then recrystallized from ethyl acetate-n-hexane, yielding 29 g of 2-(3,5-di-t-butyl-4-hydroxyphenyl)-6-hydroxybenzthiazole in the form of colorless acicular crystals.

Melting point: 289-291°C (decomposition)

Embodiment 175

A 3.1 g quantity of 2-(2-thienyl)-6-methoxybenzimidazole was added to 40 mL of 47 percent hydrobromic acid aqueous solution and the mixture was stirred with heating for 3 hours. After cooling, the precipitating crystals were collected by filtration, suspended in water, and neutralized with sodium carbonate. The precipitating crystals were collected by filtration, washed with water, and dried. the crystals were recrystallized from ethanol-n-hexane, yielding 2.6 g of 2-(2-thienyl)-6-hydroxybenzimidazole in the form of a pale yellow powder.

Melting point: 202-205°C

Embodiment 176

A methylene chloride solution (1 M solution, 82 mL) of BBr_3 was added dropwise with ice cooling to 40 mL of a methylene chloride solution of 4 g of 2-(2-methoxyphenyl)-6-trifluoromethylbenzimidazole. The mixture was hot refluxed for 15 hours, poured into ice water, neutralized with sodium hydroxide solution, extracted with an 8:1 mixture of chloroform:methanol, washed with water, and dried (sodium sulfate). Following concentration under reduced pressure, the residue was refined by silica gel chromatography (methylene chloride) and recrystallized from diethylether-n-hexane, yielding 0.8 g of 2-(2-hydroxyphenyl)-6-trifluoromethylbenzimidazole in the form of a white powder.

Melting point: 264.5-265.5°C

The compounds of Embodiments 28, 31, 32, 56, 57, 59-69, 77, 78, 79, 84, 90, 115, 116, 118, 121, and 123 were obtained using suitable starting materials in the same manner as in Embodiments 173-176.

Embodiment 177

A 0.4 g quantity of 2-(4-carbobenzyloxypiperazinyl)-6-(o-chlorobenzylamino)benzthiazole was added to 50 mL of 1 N hydrochloric acid and the mixture was hot refluxed for 18 hours. After cooling, the mixture was rendered alkaline with a sodium hydroxide aqueous solution and extracted with chloroform. The chloroform layer was washed with water and dried (sodium sulfate). The solvent was distilled off under reduced pressure. The residue was refined by silica gel chromatography (chloroform:methanol = 8:1), hydrochloric acid/methanol were added, and the mixture was concentrated. The mixture was then recrystallized from ethanol-diethylether, yielding 0.15 g of 2-piperazinyl-6-(o-chlorobenzylamino)benzthiazole hydrochloride in the form of a pale yellow powder.

Melting point: 215-218°C (decomposition)

Embodiment 178

A 1.5 g quantity of 2-(4-hydroxy-3,5-di-t-butylphenyl)benzthiazole was added to 20 mL of methanesulfonic acid and the mixture was stirred for 4 days at 90-100°C. The mixture was poured into water and extracted with chloroform. The chloroform layer was washed with water and dried (sodium sulfate). The solvent was distilled off under reduced pressure. The residue was refined by silica gel chromatography (methylene chloride) and recrystallized from ethyl acetate-n-hexane, yielding 0.45 g of 2-(4-hydorxy-3-t-butylphenyl)benzthiazole in the form of pale yellow acicular crystals.

Melting point: 189-192°C (decomposition)

Embodiment 179

A 1.1 g quantity of 2-(2-pyrrolyl)-6-ethoxybenzthiazole was dissolved in 15 mL of dimethylformamide. While cooling with ice, 0.22 g of sodium hydride (60 percent oil) was added. The mixture was stirred for 0.5 hour at room temperature, 0.7 g of methyl iodide was added, and the mixture was stirred overnight at room temperature. Water was added, the mixture was extracted with chloroform, and the chloroform layer was washed with water and dried (sodium sulfate). The solvent was distilled off under reduced pressure. The residue was refined by silica gel chromatography (methylene chloride) and recrystallized from n-hexane, yielding 0.4 g of 2-[2-(N-methyl)pyrrolyl]-6-ethoxybenzthiazole in the form of colorless acicular crystals.

Melting point: 87-88°C

The compounds of Embodiments 79, 80, 81, 82, and 84 were obtained using suitable starting materials in the same manner as in Embodiment 179.

Method of screening for blood platelet adhesion

The present method essentially consisted of quantifying the degree of adhesion of blood platelets to collagen fiber under conditions preventing a coagulation reaction in vitro. Blood was collected from healthy persons with normal blood platelet function by adding 0.1 percent ethylenediaminetetracetic acid disodium salt (EDTA·4Na) and the platelet rich plasma (PRP) was rapidly separated. Next, the PRP was washed twice with Tyrode's buffer (50 mM Tris, 0.1 percent EDTA, Ca(-), Mg(-), 0.14 percent BAS added, pH 7.4). The platelet count was adjusted to 300,000/μL with the same buffer to obtain a suspension (EDTA-WP). The collagen solution employed was obtained by dissolving 4 mg of type I (derived from bovine skin) made by Sigma in 0.25 mL of 83.5 mM acetic acid, adding 8 mL of distilled water, conducting ultrasonic suspension for 2 minutes at 4°C, and collecting 5 mL of the supernatant. To the extent permitted, the compounds were dissolved in dimethylformamide (DMF) to a concentration of 2×10^{-2} M or greater. Normally, the platelet coagulation tracers (Niko Bioscience) employed in methods of measuring the platelet coagulation function were used and the change in turbidity of the free platelet solution was recorded as the change in the amount of light passing through a glass cuvette to measure the degree of adhesion of the platelets. The change was traced at a sensitivity (20 mV) of five times the normal sensitivity of the recording device. A 200 μL quantity of EDTA-WP was introduced into an auxiliary glass cuvette, 1 μL of compound solution was added, the mixture was incubated for 5 minutes at room temperature, the cuvette was placed on the platelet tracer, one minute was allowed to pass to allow a temperature of 37°C to be reached, about 20 μL (50 μg/mL) of collagen solution was added, and the degree of platelet adhesion was measured.

The inhibition rate percentage was calculated by the following method:

transmittance of control group - transmittance of group administered drug

Inhibition rate (%) = $\frac{\text{transmittance of control group}}{\text{transmittance of control group}} \times 100$

The results are given in Table 4.

Numbers of the compounds tested:

1. 2-(1-Piperazinyl)-6-chlorobenzthiazole hydrochloride

2. 2-(3,5-Dimethyl-1-piperazinyl)-6-chlorobenzthiazole hydrochloride

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3. 2-(4-Amino-1-piperidinyl)-4,6-dichlorobenzthiazole 2 hydrochloride

4. 2-(4-Acetylamino-1-piperidinyl)-6-ethoxycarbonylmethoxybenzthiazole

5. 2-[4-(1-Piperidinyl)-1-piperidinyl]-6-chlorobenzthiazole

6. 2-(4-Dimethylamino-1-piperidinyl)-4-methyl-6-chlorobenzthiazole 2 hydrochloride

7. 2-(4-Dimethylamino-1-piperidinyl)-6-(2-chlorobenzyloxy)benzthiazole hydrochloride

8. 2-(4-Dimethylamino-1-piperidinyl)-5-(2-chlorobenzylamino)-6-ethoxybenzthiazole

9. 2-(4-Dimethylamino-1-piperidinyl)-4-[N-(2-chlorobenzyl)-N-acetylamino]-6-(2-chlorobenzyloxy)benzthiazole

10. 2-(2-Methoxyphenyl)-6-hydroxybenzthiazole

11. 2-(2-Methoxyphenyl)-6-[N-(3-dimethylaminopropyl)-N-ethylamino]benzthiazole oxalate

12. 2-(2-Methoxyphenyl)-6-[3-[N,N-bis(2-hydroxyethyl)amino]propoxy]benzthiazole

13. 2-(2-Methoxymethyl-1-pyrrolidinyl)propoxy]benzthiazole

14. 2-(2-Methoxyphenyl)-6-(3,5-di-t-butyl-4-hydroxybenzyloxy)benzthiazole

15. 2-(2-Methoxyphenyl)-6-(3-dimethylaminopropoxy)-7-(3,5-di-t-butyl-4-hydroxybenzyl)benzthiazole

16. 2-(2-Methoxyphenyl)-6-[N'-(2-chlorobenzyl)amidino]benzthiazole

17. 2-[2-(3-Dimethylaminopropoxy)phenyl]-5-nitrobenzthiazole oxalate

18. 2-[2-(2-Dimethylaminoethoxy)phenyl]-6-chlorobenzthizaole

19. 2-[2-[3-(1-Piperidinyl)propoxy]phenyl]-6-chlorobenzthiazole oxalate

20. 2-[2-(3-Cyclohexylaminopropoxy)phenyl]-6-chlorobenzthiazole

21. 2-(2-Chlorophenyl)-6-(3-dimethylaminopropoxy)benzthiazole oxalate

22. 2-(3,5-Di-t-butyl-4-hydroxyphenyl)-6-methoxybenzthiazole

23. 2-(3,5-Di-t-butyl-4-hydroxyphenyl)-6-[3-(N-methyl-N-cyclopropylamino)propoxy]benzthiazole

24. 2-(3,5-Di-t-butyl-4-hydroxyphenyl)-6-[3-(2α-hydroxymethyl-1-pyrrolidinyl)propoxy]benzthiazole

25. 2-(3,5-Di-t-butyl-4-hydroxyphenyl)-6-(3-amidinopropoxy)benzthiazole hydrochloride

26. 2-(3,5-Di-t-butyl-4-hydroxyphenyl)-6-[3-(N',N'-dimethylamidino)propoxy]benzthiazole hydrochloride

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27. 2-(3,5-Di-t-butyl-4-hydroxyphenyl)-4-[3-(4-dimethylamino-1-piperidinyl)propoxy]benzthiazole

28. 2-(3,5-Di-t-butyl-4-hydroxyphenyl)-6-[3-(4-dimethylamino-1-piperidinyl)propoxy]benzthiazole

29. 2-(3,5-Di-t-butyl-4-hydroxyphenyl)-5-[3-(4-dimethylamino-1-piperidinyl)propoxy]benzthiazole

30. 2-(4-Methoxy-3-t-butylphenyl)-6-hydroxymethylbenzthiazole

31. 2-(4-Methoxy-3-t-butylphenyl)-6-aminobenzthiazole

32. 2-(4-Methoxy-3-t-butylphenyl)-6-(2β-hydroxymethyl-1-pyrrolidinyl)methyl]benzthiazole

33. 2-(4-Methoxy-3-t-butylphenyl)-6-[3-(4-dimethylamino-1-piperdinyl)propylamino]benzthiazole 2 fumarate

34. 2-(4-Methoxy-3-t-butylphenyl)-6-(3-dimethylaminopropanoylamino)benzthiazole

35. 2-(4-Methoxy-3-t-butylphenyl)-6-[3-(4-dimethylamino-1-piperidinyl)propanoylamino]benzthiazole

36. 2-(4-Methoxy-3-t-butylphenyl)benzthiazole

37. 2-(1-Methyl-2-pyrrolyl)-6-hydroxybenzthiazole

38. 2-(1-Methyl-2-pyrrolyl)-6-dimethylaminothiocarbonyloxybenzthiazole

39. 2-(1-Methyl-2-pyrrolyl)-6-dimethylaminocarbonylthiobenzthiazole

40. 2-(2-Pyrrolyl)-6-[3-(2α-dimethylaminocarbonyl-1-pyrrolidinyl)propoxy]benzthiazole

41. 2-(1-Pentyl-2-pyrrolyyl)-6-hydroxybenzthiazole

42. 2-(2-Thienyl)benzthiazole

43. 2-(2-Methoxyphenyl)-6-trifluoromethylbenzthiazole

44. 2-(2-Hydroxyphenyl)-6-trifuloromethylbenzimidazole

45. 2-(3,5-Di-t-butyl-4-hydroxyphenyl)-6-chlorobenzimidazole

46. 1-Ethyl-2-(3,5-di-t-butyl-4-hydroxyphenyl)-6-chlorbenzthiazole

47. 2-(3-Chloroanilino)-6-trifluoromethylbenzimidazole oxalate

48. 2-(3-Trifluoromethylanilino)-6-trifluoromethylbenzimidazole

49. 2-(3-Methylthioanilino)-6-trifluoromethylbenzthiazole oxalate

50. 2-(N-Methyl-3-chloroanilino)-6-trifluoromethylbenzimidazole

51. 2-(2-Pyridylthiomethyl)-6-chlorobenzimidazole hydrochloride

52. 2-(2-Thienyl)-6-trifluoromethylbenzimidazole

53. 2-(2-Thienyl)-6-(1-pyrrolidinyl)benzimidazole

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54. 2-(2-Thienyl)-6-(1-pyrrolyl)benzimidazole

55. 2-(2-Thienyl)-6-[3-(5-cyclohexyl-2-furyl)propoxy]benzthiazole

56. 2-(2-Thienyl)-6-(dimethylanocarbonylthio)benzimidazole

57. 1-Methyl-2-(2-thienyl)-6-chlorobenzimidazole

58. 1-Allyl-2-(2-thienyl)-6-trifluoromethylbenzimidazole

59. 1-Pentyl-2-(2-thienyl)-6-trifluoromethylbenzimidazole

60. 1-Benzyl-2-(2-thienyl)-6-chlorobenzimidazole

Table 4

Test compound	Adhesion inhibition rate (%)	
	Concentration (moles)	
	1×10^{-4}	3×10^{-5}
1	78.95	-
2	83.65	-
3	94.80	-
4	64.80	-
5	83.10	-
6	-	80.70
7	-	84.95
8	-	74.50
9	-	58.75
10	-	56.05
11	-	73.10
12	-	49.90
13	-	66.35
14	-	56.40
15	-	78.30

Test compound	Adhesion inhibition rate (%)	
	Concentration (moles)	
	1×10^{-4}	3×10^{-5}
16	-	69.75
17	-	76.60
18	-	79.15
19	-	79.40
20	-	78.05
21	-	63.15
22	-	55.55
23	-	76.75
24	-	86.90
25	-	46.80
26	-	83.45
27	-	76.65
28	-	98.80
29	-	89.80
30	-	55.75
31	-	52.20

Test compound	Adhesion inhibition rate (%)	
	Concentration (moles)	
	1×10^{-4}	3×10^{-5}
32	-	74.50
33	-	95.90
34	-	79.25
35	-	88.85
36	-	71.60
37	-	61.65
38	-	41.95
39	-	47.65
40	-	40.80

41	-	50.85
42	-	42.40
43	-	50.65
44	-	41.40
45	-	44.55
46	-	53.80
47	-	60.35

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Test compound	Adhesion inhibition rate (%)	
	Concentration (moles)	
	1×10^{-4}	3×10^{-5}
48	-	54.20
49	-	63.90
50	-	42.90
51	-	47.55
52	-	62.20
53	-	40.45
54	-	46.50
55	-	40.95
56	-	56.95
57	-	44.00
58	-	48.10
59	-	58.75
60	-	46.25